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TOXOPLASMIC ENCEPHALOMYELITIS

VI. CLINICAL DIAGNOSIS OF INFANTILE OR CONGENITAL TOXOPLASMOSIS; SURVIVAL BEYOND INFANCY

DAVID COWEN, M.D.

ABNER WOLF, M.D.

AND

BERYL H. PAIGE, M.D.

NEW YORK

Cases of infantile toxoplasmic encephalomyelitis, an infection of the central nervous system due to the protozoon Toxoplasma, have thus far been recognized only by postmortem study [1] and animal inoculation with infected tissues obtained at autopsy.[2] Consideration of some of the outstanding pathologic features of the disease and a review of the clinical findings in cases verified by autopsy have suggested certain diagnostic criteria for the recognition of the disease during life.[1] The outstanding clinical features are the appearance of symptoms and signs of widespread involvement of the central nervous system, often marked by internal hydrocephalus and convulsions at birth, or

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From the Departments of Neurology and Pathology, Columbia University College of Physicians and Surgeons; the Neurological Institute, and the Babies Hospital.

1. (*a*) Wolf, A., and Cowen, D.: Granulomatous Encephalomyelitis Due to an Encephalitozoon (Encephalitozoic Encephalomyelitis), Bull. Neurol. Inst. New York **6**:306-371, 1937; Granulomatous Encephalomyelitis Due to a Protozoan (Toxoplasma or Encephalitozoon): II. Identification of a Case from the Literature, ibid. **7**:266-290, 1938. (*b*) Wolf, A.; Cowen, D., and Paige, B. H.: Toxoplasmic Encephalomyelitis, Am. J. Path. **15**:657-694, 1939. (*c*) Paige, B. H.; Cowen, D., and Wolf, A.: Toxoplasmic Encephalomyelitis: V. Further Observations of Infantile Toxoplasmosis; Intrauterine Inception of the Disease; Visceral Manifestations, Am. J. Dis. Child. **63**:474-514 (Jan.) 1942.

2. Wolf, A.; Cowen, D., and Paige, B. H.: Human Toxoplasmosis: Occurrence in Infants as an Encephalomyelitis; Verification by Transmission to Animals, Science **89**:226-227, 1939; Toxoplasmic Encephalomyelitis: IV. Experimental Transmission of the Infection to Animals from a Human Infant, J. Exper. Med. **71**:187-214, 1940.

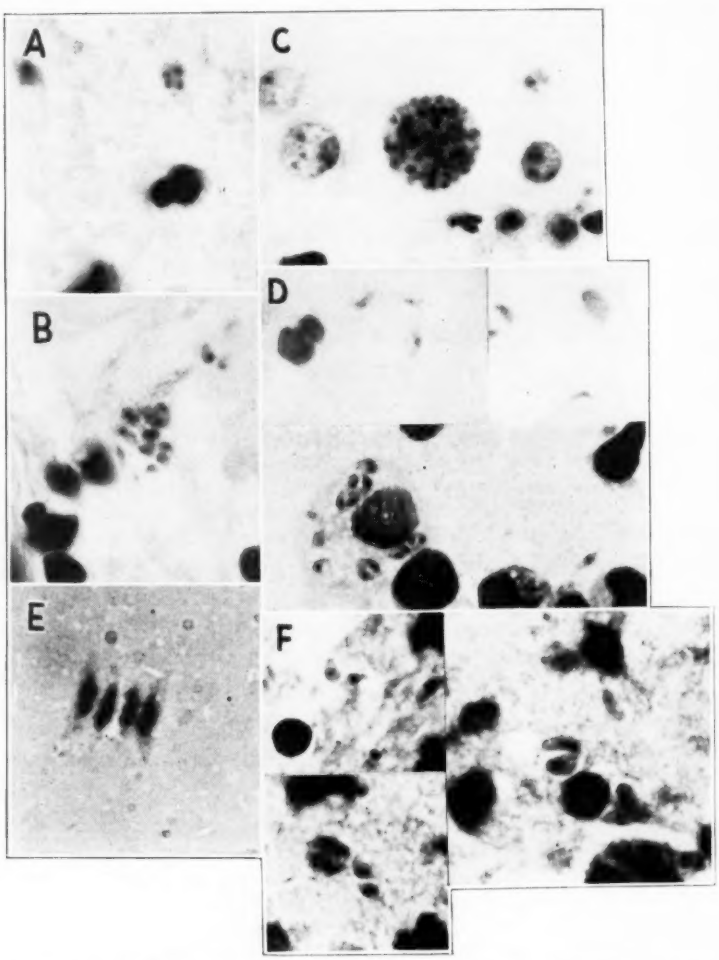

Fig. 1.—*A,* cluster of toxoplasmas in cerebral lesion of an infant. Note oval bodies and eccentric, deeply staining, rounded nucleus of the parasite. Phloxine-hematoxylin stain.

B, free toxoplasmas in retinal lesion of an infant. Phloxine-hematoxylin stain.

C, parasitic "cyst" in cerebral lesion of an infant. Note close approximation of parasites, indefinite margins of individual organisms and lack of well formed surrounding membrane. Phloxine-hematoxylin stain.

D, free and intracellular toxoplasmas in smear of peritoneal fluid of a mouse infected with the human BD strain of Toxoplasma. Note crescentic or fusiform shape and central or eccentric nucleus. Wright-Giemsa stain.

E (case 1; P. D.), toxoplasmas in smear of cerebrospinal fluid. Wright-Giemsa stain.

F, toxoplasmas in cerebral lesions of mouse inoculated with cerebrospinal fluid from case 2, J. F. Hematoxylin-eosin stain.

soon thereafter; roentgenographic evidence of cerebral calcification, and characteristic focal chorioretinitis. Since the description of the pathologic material, 6 living patients have been encountered who show some or all of the features of the syndrome so outlined. From some of these infants and children, toxoplasmas have been isolated, and for these and for all the others serologic reactions have proved positive. An acute, juvenile form of toxoplasmic encephalitis has been reported recently.[3] The clinical picture would appear to be quite unlike that seen in either the early phases of the infantile form or in the children with the chronic form who survive into the juvenile period. These differences will be discussed later. Adult toxoplasmosis has also been described,[4] and the predominantly pulmonary infection differentiates it clinically from most instances of infantile toxoplasmosis. This will also be referred to later.

The morphologic and biologic characteristics of the parasite, Toxoplasma, have been described in previous reports[5] (fig. 1).

REPORT OF CASES

CASE 1.—P. D., a white girl 3 years 9 months of age, was admitted to the Neurological Institute of New York on Jan. 20, 1941 because of "epileptic fits," which had begun at the age of 5 months.

Family History.—The father, 33 years old, was born in Poughkeepsie, N. Y., and had never traveled outside of the state. On two occasions before the birth of the patient the father had had an indeterminate type of infection of the respiratory tract during the summer, possibly mild pneumonia. After the birth of the patient there were several additional attacks, the last of which, at least, proved to be clearcut lobar pneumonia, due to Pneumococcus. The mother, 30 years of age, was born in New York city and had lived there all her life except for occasional travel in New York state. Aside from an attack of diphtheria and an eruption on the back of the arms, she had always been in good health. The first child of the union was born two years after the marriage. She is at present 10 years old and, with the exception of occasional attacks of abdominal pain believed to be due to mesenteric lymphadenitis, has been entirely normal mentally and physically. The second child (P. D.) was born eight years after marriage. Both parents had had various contacts with common animals. As a girl, the mother had a parrot and cats in the home. Eight years before the birth of the patient the couple kept a canary, and three years before her birth they had a pet poodle, which occasionally had had "fits," with frothing at the mouth and shaking of the limbs. At one time the home was infested with mice, requiring the use of traps and vermicide, and "field mice" had at times been seen in their food stores. There had been no known contact with rabbits, nor had rabbit meat been eaten.

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3. Sabin, A. B.: Toxoplasmic Encephalitis in Children, J. A. M. A. **116**:801-807 (March 1) 1941.

4. (*a*) Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, Arch. Path. **30**:374-392 (July) 1940. (*b*) Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: A Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, J. A. M. A. **116**:807-814 (March 1) 1941.

5. Wolf, Cowen and Paige (footnotes 1 *b* and 2).

During her pregnancy with the patient the mother was apparently well, and the Wassermann reaction of her blood was negative. The membranes ruptured twenty-two hours before the onset of labor. Birth was one month premature and was spontaneous, after a labor of twenty-six hours. The postpartum course was uneventful. A record of the appearance of the placenta was not available.

Personal History.—At birth the infant's condition was satisfactory. The weight was 4 pounds 12 ounces (2,150 Gm.). She was fed on a formula from the beginning, but took feeding poorly. Vomiting occurred frequently, and there appeared to be difficulty in sucking and swallowing, requiring the use of a nipple with a large hole. She frequently refused orange juice, cereals and vegetables and at 1 year of age was found to have scurvy and rickets, which were treated by the administration of ascorbic acid and cod liver oil. The mother stated that the infant's eyesight had been "poor" since birth and that the left eye had "turned upward" since the age of 5 months. She held up her head at 10 months of age, sat up at 14 months and walked at 19 months. Dentition began at 11 months, and she acquired bowel and bladder control at 2½ years of age. The child never learned to talk. Attacks of "pneumonia," the last accompanied by streptococcic pharyngitis and otitis media, occurred at the ages of 1, 2 and 3 years. Bottle feeding was continued until after the age of 3 years, after which the child was with difficulty induced to take solid foods. At the age of 5 months she had her first convulsive seizure, characterized by loss of consciousness, generalized rigidity, rolling up of the eyes and foaming at the mouth. This attack lasted about fifteen minutes and was followed by several hours of sleep. After the initial seizure, convulsions occurred once every two or three months. They were usually preceded by vomiting. A particularly severe attack, at the age of 3 years, was associated with unconsciousness for five hours. Roentgenographic examination of the skull at this time revealed small areas of calcification in both parietal regions, interpreted as calcified subdural hematomas. At this time the patient had not yet learned to speak, although she was able to make unintelligible sounds and to understand what was said to her. At 3½ years of age the patient was hospitalized and ventriculography revealed internal hydrocephalus, which was thought to be the result of noninflammatory obstruction of the aqueduct of Sylvius. The Kline and Mantoux reactions were negative. The fundi of both eyes showed areas of scarring and pigmentation, which were interpreted as possible colobomas of the choroid or as chorioretinitis.

Physical Examination (age, 3 years 9 months).—The child was somewhat asthenic, hyperactive and uncooperative. She weighed 32 pounds 6 ounces (14.6 Kg.). No intelligible words were spoken, but simple commands were understood. Responses were made by gestures and grunts. The circumference of the head was 45 cm. Gait and muscle strength were normal. There was slight clumsiness in the use of the left hand. The deep reflexes were active and approximately equal on the two sides. There was an equivocal Babinski reflex on the left side. A few small lymph nodes were palpable in the anterior cervical region. The heart and lungs were normal. The liver and spleen could not be felt. The body temperature was normal.

Ophthalmologic Examination.—Central vision appeared to be lacking, and there was searching nystagmus. The right pupil was slightly larger than the left, and both pupils were somewhat sluggish in response to illumination, both consensual and direct.

Fundi: The media were clear. The optic disks were pale and atrophic, the right more so than the left. Two large patches of old healed chorioretinitis were seen in the right fundus. The smaller lesion was irregularly round, well demarcated and approximately 1.5 disk diameters in diameter and was centered on the

macular region. The surface of the lesion was slightly depressed below the level of the adjacent retina. Within this lesion there were small patches of complete choroidal atrophy, so that the sclera shone through. The area showed irregular deposition of much brownish black pigment. Retinal structures were no longer

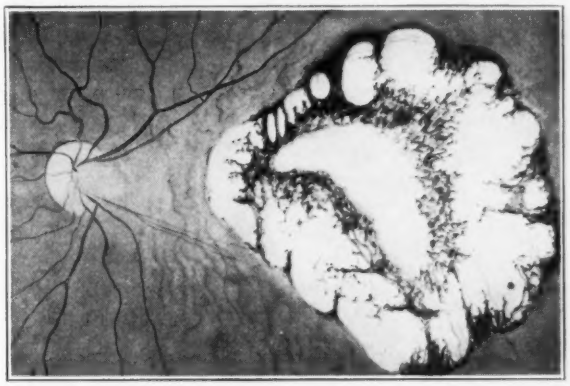

Fig. 2 (case 1; P. D.).—Photograph of drawing of left eyeground. A large patch of old healed chorioretinitis involves the macular area. Note atrophy and pigmentation. A poorly defined lesion involves the temporal aspect of the atrophic disk.

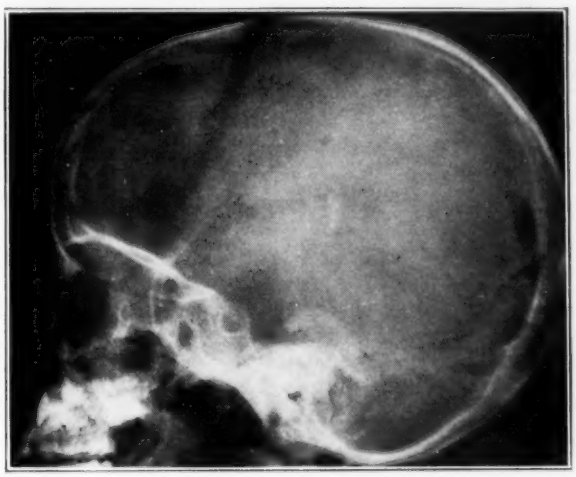

Fig. 3 (case 1; P. D.).—Roentgenogram of skull, showing separation of coronal suture. Note two comma-shaped areas of calcification, apparently in the thalami.

identifiable within it, and there was no evidence of inflammatory activity. The second lesion in the right eye was oval, sharply outlined and about 4 disk diameters wide and was situated in the upper nasal quadrant. It was similar to the first lesion and contained deposits of black pigment, particularly over its base and toward the periphery. The choroid and retina at the site of this lesion were completely atrophic, aside from some straight choroidal arteries which traversed the base, and only yellowish white sclera remained. The lesion in the left eye

was large, somewhat triangular and central in position and measured 6 disk diameters in diameter (fig. 2). Its margins were scalloped and contained heavy deposits of black pigment, which were scattered throughout the lesion as well. Some choroidal vascular channels persisted in the floor of this patch. A gray, homogeneous, elevated mass of proliferated glial tissue was present in the center of the lesion. Elsewhere the color was that of the yellowish white, glistening sclera. A poorly defined extension of the main lesion passed from its nasal margin to the temporal margin of the atrophic disk. This appeared as a somewhat elevated, finely granular, reddish brown band, obscuring the juxtapapillary portion of the retina. The remaining portions of the retina and choroid of each eye were entirely normal.

Roentgenographic Examination of the Skull.—The sagittal and coronal sutures were somewhat separated, and the posterior clinoid processes and dorsum sellae were atrophied. There were two comma-shaped areas of calcification, which on stereoscopic examination appeared to be situated in the thalami (fig. 3).

Ventriculography and Encephalography.—The lateral ventricles were considerably enlarged, the atrial portions and the occipital and temporal horns being more involved than the frontal horns and the anterior portion of the bodies (fig. 4 *A* and *B*). The left occipital horn was extremely dilated, and sharp concavities were seen in the superior margin of the tip of each temporal horn. The fourth ventricle was normal in size, shape and position, while the aqueduct was slightly enlarged.

Laboratory Data.—Ventricular Fluid: The pressure was increased and slightly turbid. Culture yielded no growth. A cell count revealed 3 white blood cells and 700 red blood cells per cubic millimeter.

Spinal Fluid: The fluid was cloudy and slightly xanthochromic. Culture yielded no growth. The total protein was 19 mg. per hundred cubic centimeters. The first cell count revealed 1,100 red cells and 1,435 white cells per cubic millimeter, 80 per cent of which were polymorphonuclear leukocytes and 20 per cent lymphocytes; the second count, 14,000 red cells and 523 white cells per cubic millimeter, of which 51 per cent were polymorphonuclear leukocytes and 49 per cent lymphocytes; the third count, 700 red cells and 197 white cells per cubic millimeter, of which 16 per cent were polymorphonuclear leukocytes and 84 per cent lymphocytes, and the fourth count, 693 red cells and 3 white cells per cubic millimeter.

Blood Count: The hemoglobin concentration was 88 per cent; the red cells numbered 4,300,000 and the white cells 10,850 per cubic millimeter, with 47 per cent polymorphonuclear leukocytes, 49 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils.

Urinalysis: The urine was normal.

Psychometric Status.—Examination at 3 years and 9 months of age showed the patient to be definitely retarded, her responses being those of a 2½ year old child.

Course.—After discharge from the hospital, there was continued evidence of increased intracranial pressure, with bulging of the scalp at the site of the ventriculographic trephine defect in the skull. Periods of drowsiness, lasting a few hours or days, occurred from time to time, and on one occasion the child was found semicomatose on the floor, presumably after a convulsive seizure. Recovery from this episode was uneventful. There has been no improvement in vision or in speech development. The child is overactive and unruly. She is now 5 years of age.

Attempts to Diagnose Toxoplasmosis by Laboratory Methods.—A. Animal Inoculation: Repeated attempts to isolate Toxoplasma by the inoculation of animals

with spinal and ventricular fluid have proved unsuccessful in this case. A total of 20 mice (inoculated intraperitoneally and intracerebrally), 2 guinea pigs (inoculated intracardially and intracerebrally) and 1 rabbit (inoculated intravenously and intracerebrally) were used in these trials. The animals were observed over a period of two to four months, and none showed evidence of having acquired

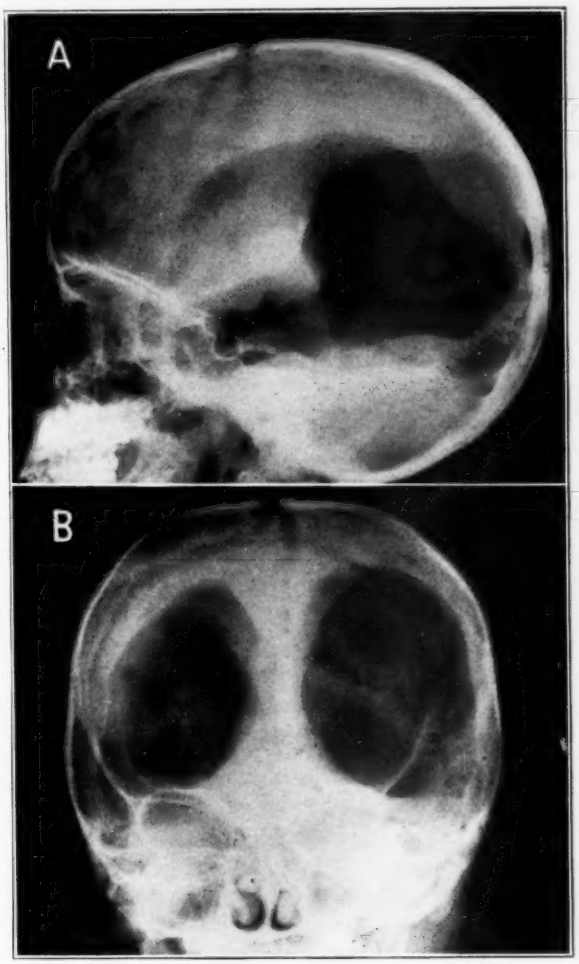

Fig. 4 (case 1; P. D.).—*A*, lateral ventriculogram of skull, showing enlargement of lateral ventricles and calcification in thalamus.

B, posteroanterior ventriculogram of skull, showing enlargement of lateral ventricles.

toxoplasmosis. In many instances, histologic examination of the tissues was made, and this also proved negative. Inoculation of the patient's blood into animals on two occasions (13 mice, 1 rabbit and 1 guinea pig) was also unsuccessful.

B. Smears of Cerebrospinal Fluid: Ventricular fluid removed on Oct. 14, 1940 [6] was centrifuged and the sediment smeared, fixed in methyl alcohol and stained by the Wright-Giemsa method. Scattered clusters of three or four slender, lunate or slightly curved organisms, with faintly eosinophilic cytoplasm and central, hyperchromatic nuclei, were present in small numbers (fig. 1 *E*).

C. Serum Neutralization Tests: The patient's serum was tested three times at the age of 3 years 10 months by the method described later for antibodies to Toxoplasma. On two occasions the result was positive, and on one it was suggestively positive. The serums of the mother and father were examined and found to be negative (table 1).

Summary.—A white girl, 3 years 9 months of age, was admitted to the hospital because of "epileptic fits," which had started in infancy. Her eyesight was said to have been poor from birth. In early life there were vomiting, difficulty in sucking and swallowing and frequent refusal of food. Coincident with the onset of convulsions, at 5 months of age, strabismus of the left eye was noted. Generalized epileptic seizures occurred every few months, tending to decrease in frequency as the child grew older. At the age of 3 years small areas of intracerebral calcification were first observed by roentgenographic examination. At 3½ years of age ventriculographic studies disclosed pronounced internal hydrocephalus, thought to be the result of obstruction of the aqueduct of Sylvius. The eyegrounds contained focal areas of scarring and pigmentation bilaterally, resulting from old chorioretinitis. The cerebrospinal fluid was xanthochromic and showed a variable degree of pleocytosis. Episodes of increased intracranial pressure associated with drowsiness occurred from time to time. The child remained mentally retarded, and speech was noticeably defective. In one examination of ventricular fluid a few small clusters of toxoplasmas were seen in smears. Neutralizing antibodies to Toxoplasma were demonstrated in the patient's serum but were absent in the serums of the father and mother.

Case 2.—J. F., a white boy, was born at Sloane Hospital, Feb. 2, 1941, and was transferred to Babies Hospital because of jaundice and hydrocephalus.

Family History.—The father, a cab driver, 30 years of age, was born in Italy, came to the United States as a child, lived for a time in Connecticut and then settled in New York city. His health was satisfactory. There had been no contacts with animals except various pet dogs. The mother, 25 years of age, was born and had always lived in New York city except for a short visit to Connecticut. She had kept no pets as a girl and had never eaten rabbit meat. She did not recall having had any serious illness. The first child of the union, born nineteen months before the patient, was normal in health and development. During pregnancy with the patient (J. F.) the mother's condition was good. At this time the couple lived in a home free of mice and rats. A pet dog, kept for a few weeks, became "wild" and was disposed of during the eighth month of the mother's pregnancy. The membranes were intact until the onset of labor. Delivery occurred

6. This fluid was removed at the New York Hospital and given to us for examination.

spontaneously at term after a labor of about two hours. The placenta was described as normal and was not further examined. The postpartum course was normal.

Personal History and Clinical Observations.—The infant was in good condition at birth. Respirations began spontaneously, and there was no evidence of birth injury. The initial weight was 3,430 Gm. and the height 49 cm. The skin and scleras were slightly jaundiced. The liver and spleen were not palpable. The blood count (hemoglobin content 18.2 Gm. per hundred cubic centimeters; red cells 5,860,000 and white cells 15,000 per cubic millimeter, with 72 per cent polymorphonuclear leukocytes, 21 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils) and the temperature were normal. At the age of 9 days a transient scattered, maculopapular rash was observed and brisk hemorrhage occurred from the umbilical cord. The plasma prothrombin time was found to be considerably elevated. Administration of vitamin K, as menadione (2-methyl-1,4-naphthoquinone), resulted in satisfactory control of the bleeding and fall in the prothrombin time to normal. The icterus noted at birth deepened (serum bilirubin 15.32 mg. per hundred cubic centimeters—indirect, 6.8 mg.; direct, 8.5 mg.), and on the thirteenth day of life the liver and spleen were found to be enlarged. During this period the temperature and the blood picture remained normal. The serum alkaline phosphatase was elevated (16.4 Bodansky units). The stools were generally yellowish or greenish. At the age of 26 days the anterior fontanel was noted to be full and the sagittal suture separated to the posterior fontanel. The head measured 36.5 cm. in circumference (chest, 34.0 cm.), and six days later it had increased to 39.5 cm. The liver and spleen had increased in size and their borders were palpable 3 to 4 cm. below the costal margin. The usual normal reflexes for the age were present, including the grasp and Moro responses and suggestive tonic neck reflexes. A few small lymph nodes were felt in the posterior cervical regions and the axillas.

At 30 days of age the presence of hydrocephalus was confirmed by roentgenographic examination of the skull, which showed separation of the sutures and the presence of multiple areas of calcification in the cerebrum. Two large masses of calcification were seen in the region of the basal ganglia, and extensive focal calcification was present approximately in the region of the right parietal cortex. Roentgenograms of the long bones were normal.

The blood count at 1 month of age showed a hemoglobin content of 10.2 Gm. per hundred cubic centimeters (71 per cent), 3,540,000 red cells and 12,700 white cells per cubic millimeter, with 38 per cent polymorphonuclear leukocytes, 50 per cent lymphocytes, 8 per cent monocytes, 4 per cent eosinophils, and a few nucleated red blood cells. The serum bilirubin fell to 5.81 mg. per hundred cubic centimeters—indirect 2.11 mg. and direct 3.70 mg. The serum phosphorus was 5.9 mg. per hundred cubic centimeters and the phosphatase 20.8 Bodansky units. The Kline reaction of the blood was negative. A blood culture yielded no growth. Hanger's cephalin flocculation test gave negative results.

The electrocardiogram showed sinus tachycardia.

Ventricular puncture yielded xanthochromic cerebrospinal fluid. The cell count was 250 per cubic millimeter, with 88 per cent lymphocytes. Chlorides measured 652 mg., sugar 45 mg. and total proteins 110 mg. per hundred cubic centimeters. After introduction of 1.0 cc. of phenolsulfonphthalein into the ventricle, no dye was found in the lumbar fluid at the end of twenty-five minutes, indicating an obstructive type of hydrocephalus. Lumbar puncture yielded xanthochromic fluid. The cell count was 250 per cubic millimeter, with 2 per cent polymorphonuclears and 98 per cent lymphocytes. Chlorides measured 652 mg., sugar 75 mg. and total proteins 130 mg. per hundred cubic centimeters.

Ophthalmologic Examination.—There was slight left microphthalmos, the left cornea measuring 10 and the right 11 mm. in the horizontal diameter. Numerous remnants of pupillary membrane were seen in the anterior chamber of the left eye. The left pupil was slightly smaller than the right, and examination with the

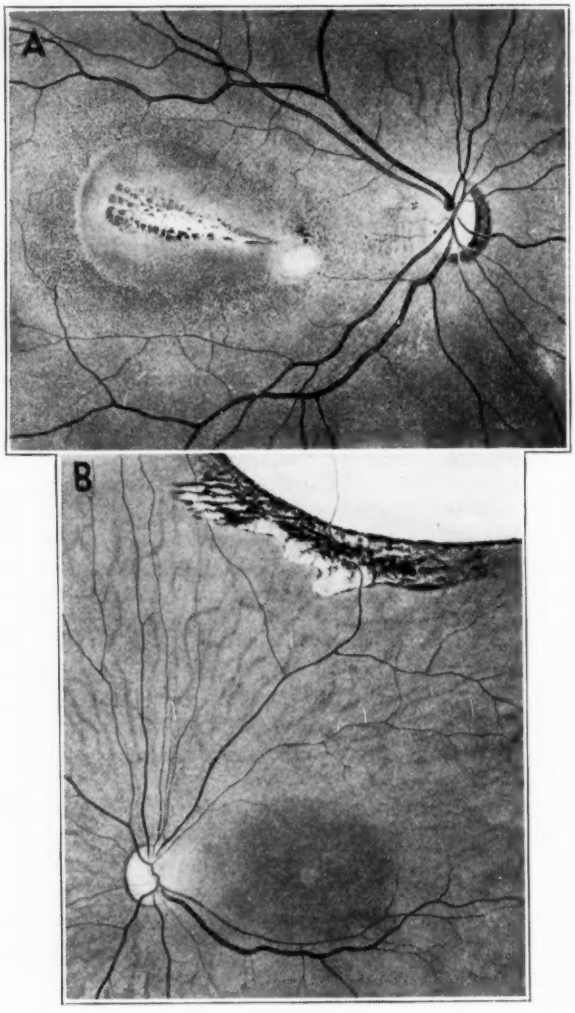

Fig. 5 (case 2; J. F.).—*A,* photograph of drawing of right eyeground. The macular lesion is somewhat more advanced than the macular lesion in the left eye and shows beginning pigmentation and atrophy.

B, photograph of drawing of left eyeground, showing oval, raised, relatively recent lesion in macular area, with umbilicated, central focus of necrosis and old healed lesion in superior quadrants.

hand loupe revealed a posterior lenticonus, which was confirmed on ophthalmoscopic examination. A small naevus flammeus was present on the left upper lid

and brow. Searching nystagmus and bilateral limitation of abduction, more pronounced in the right eye, were evident in the later examinations.

Fundi (age, 31 days): The temporal half of each disk showed low grade edema and slight hyperemia without elevation. There was active chorioretinitis in each fundus. The lesions in each eye were focal and were located in the macular region, between the superior and the inferior macular arterioles. They were marked by an egg-shaped zone of edema, measuring in the right eye approximately 4 by 2.5 disk diameters, with an elevation of 1 D., and in the left eye 4.5 by 3.5 disk diameters, with an elevation of 2 D. Nasally, each lesion closely approached the disk. The lesion in the right eye was reddish, blue-brown and was not sharply outlined (fig. 5 *A*). It was partially bordered by granular, brownish gray pigment. In this lesion toward its temporal side, there was a horizontally disposed, white, spindle-shaped area which suggested atrophy of choroidal and retinal structures, through which the sclera was revealed. Irregular deposits of black pigment were seen about this area. Two small additional yellowish, focal chorioretinal lesions were present in the juxtapapillary region on the right near the nasal end of the main lesion. In the left eye, the large area of edema was homogeneous in appearance, finely granular and reddish, blue-brown (fig. 5 *B*). Its flattened apex was slightly umbilicated and appeared to coincide with the position of the fovea.

Reexamination after a lapse of two weeks revealed, in addition to the changes described, two large chorioretinal lesions in the far periphery of the superior quadrants of the left eye which had escaped earlier observation. The smaller of the lesions was well demarcated, pale, gray-green and nonpigmented. The larger patch was a dull aquamarine and was outlined by clumps of black pigment. These foci appeared to be the oldest of all the lesions in the fundi and showed no evidence of inflammatory activity at any time.

In subsequent examinations of the eyes it was found that pigmentation increased in the chorioretinal lesions, and in the course of the next two months the centrally situated lesions became less edematous. Small, irregularly defined areas of chorioretinal atrophy, with pigmentation and residual edema, were noted in each macular region. The temporal margins of the disks were partially obscured by edema, and the disks were moderately pale, the left more so than the right. By the end of the fifth month of life inflammatory activity appeared to have completely subsided in the lesions in the right eye, while in the left eye activity subsided about a month later. The macular lesion in the right eye now occupied the whole of the originally observed egg-shaped area of edema and showed diffuse connective tissue proliferation and pigmentation. Similar changes occurred in the left eye, the entire macular region of which was the site of pigment deposition, chorioretinal atrophy and connective tissue proliferation. Optic nerve atrophy became more manifest in both eyes. The remaining portions of the retinas were normal and the media remained clear.

Course and Subsequent Examinations.—At 7 weeks of age jaundice had disappeared. The liver and spleen remained enlarged. The previously palpable cervical lymph nodes had decreased in size. The state of nutrition was satisfactory; the child gained weight, and there was no vomiting. No micro-organisms were found in material removed by puncture of the liver and spleen. The ventricular fluid at this time was clear and contained 8 cells per cubic millimeter (5 red blood cells and 3 mononuclear leukocytes). The total protein was 62.8 mg. per hundred cubic centimeters.

At the age of 8 weeks the temperature, which was previously normal, gradually rose to 101 F., respiration became accelerated and fine and sibilant rales were heard throughout both lungs. A patch of increased density appeared in the roent-

genogram of the chest, situated just above the hilus of the right lung. Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) was administered, and several days later the temperature became normal and the chest clear. Another roentgenogram of the chest showed no pathologic changes.

Encephalography and ventriculography at 2½ months of age showed that a large amount of air had entered what appeared to be the subdural space on the right side and that a small amount was in the enlarged right ventricle. The fluid obtained by lumbar puncture was clear and contained 47 cells per cubic millimeter, 52 mg. of total protein, 53 mg. of sugar and 665 mg. of chlorides per hundred cubic centimeters. The fluid removed by puncture of the fontanel, apparently from the subdural space, was orange colored, contained 12,000 red blood cells and 50 white blood cells per cubic millimeter and 268 mg. of total protein, 96 mg. of sugar and 635 mg. of chlorides per hundred cubic centimeters.

At the age of 4 months the infant was noted to have a daily rise in temperature to 100 or 101 F., reaching 103 F. on one occasion. No specific cause was determined for the fever, which disappeared spontaneously in about three weeks. Roentgenographic examination of the chest at this time showed no abnormalities. Culture of the lumbar cerebrospinal fluid yielded no bacterial growth. The head remained typically hydrocephalic in contour and now measured 44 cm. in circumference (chest, 41 cm.). When the infant was pulled upward, he was unable to support his head. The upper extremities were kept in extension most of the time. At 5½ months of age, psychometric examination showed the child to be decidedly retarded in psychomotor development, the responses being well below the 3 month level.

The child was discharged from the hospital at the age of 6 months. The blood count at this time was normal. When last examined, at the age of 7½ months, the head was still somewhat enlarged and the liver was palpable 3 fingerbreadths below the costal margin. The spleen could not be felt. The weight was 17 pounds 11 ounces (8 Kg.). Inability to abduct the right eye persisted. Aside from some difficulty in inducing the child to eat and apprehension as to his future progress, the mother was satisfied with the child's condition. He is now 14 months of age.

Attempts to Diagnose Toxoplasmosis by Laboratory Methods.—A. Animal Inoculation: Cerebrospinal fluid: Three mice were inoculated intracerebrally and intraperitoneally with ventricular fluid obtained by puncture of the fontanel when the patient was 7½ weeks of age. One of these animals became ill on the fifth day after inoculation and died on the seventh day. Histologically, the brain showed pronounced meningoencephalitis, with many toxoplasms in the lesions (fig. 1 *F*). Subinoculation of mice with a suspension of brain tissue and of material from the liver, lung and spleen resulted in typical toxoplasmosis, which was serially transmissible for fifteen generations, when passage was discontinued. The remaining 2 mice, which were inoculated with ventricular fluid, showed no histologic evidence of having become infected when examined at the end of four months. Two other attempts to infect mice with cerebrospinal fluid, 1 with ventricular fluid taken when the infant was 4½ weeks old and another with lumbar fluid taken when the child was 11½ weeks old, proved unsuccessful. Ten mice were used in each of these tests.

Blood: Inoculations of animals with citrated blood taken from the patient at the age of 5 weeks and again at 8 weeks were without effect. A total of 17 mice was used in these experiments. The animals were inoculated intraperitoneally, intravenously or by the combined intraperitoneal and intravenous routes. In addition, 2 guinea pigs were inoculated intracardially. In none of the animals did symptoms of toxoplasmosis develop during an observation period of weeks or

months. Histologic examination of their tissues was made in many instances and revealed nothing significant. Four of the mice found dead one week after inoculation with blood were free of Toxoplasma and of lesions on histologic study, and subinoculation of additional animals with their tissues was without effect.

B. Smears of Cerebrospinal Fluid: Several attempts to demonstrate toxoplasmas in smears stained by the Wright-Giemsa method were unsuccessful.

C. Serum Neutralization Test: A test for neutralizing antibodies to Toxoplasma in the patient's serum at the age of 8 months by the method to be described later gave positive results. The mother's serum, similarly examined, gave a suggestively positive reaction (table 1).

Summary.—A boy, born at full term, was jaundiced at birth, and shortly enlargement of the liver and spleen developed. Separation of the cranial sutures and fulness of the anterior fontanel were observed at 26 days of age. Roentgenographic examination of the skull confirmed the presence of internal hydrocephalus and, in addition, demonstrated a number of areas of calcification in the cerebrum. At the age of 31 days ophthalmoscopic examination disclosed multiple foci of chorioretinitis in both eyegrounds. There was slight left microphthalmos. The cerebrospinal fluid proved to be xanthochromic and showed an increase in total protein and cells. Jaundice disappeared at 7 weeks of age. The spleen was no longer felt at 7½ months of age, while the liver was still palpable. The head remained hydrocephalic, and the child appeared to be seriously retarded in psychomotor development. Inoculation of mice with cerebrospinal fluid resulted in the development in 1 mouse of toxoplasmosis, which could be transmitted serially. Similar attempts to isolate the protozoon from the blood were unsuccessful but neutralizing antibodies to Toxoplasma were present in the serum. The test of the mother's serum for such antibodies gave a suggestively positive result.

CASE 3.—A. I., a white boy aged 2 years, was admitted to the Neurological Institute on March 14, 1941, with the complaint of a "small head" and "bad eyes."

Family History.—The father was an American-born printer, 26 years of age, whose youth had been spent on a farm. Here the usual barnyard animals, including pigs, chickens, a horse and a dog, had been maintained. When the father was about 15 years of age canaries had been bred in his home. These birds were infested by "lice," and in some birds a "boil" developed above the anal region, after which they invariably died. Later he raised a setter, which eventually died of "distemper." For a time the father had traveled extensively on the eastern seaboard. His health was good. The reaction to the Kline test was negative. The mother, who had lived in New York city all her life, was 21 years of age and was also in good health. Repeated Wassermann tests of her blood gave negative results. As a girl, she had frequently eaten rabbit meat in the form of *Hasenpfeffer,* and for a short while kept a pet canary in the house. During the mother's pregnancy the couple lived in a home badly infested with vermin. Roaches, fleas, "centipedes" and black, "hard-backed" bugs "with many legs" were numerous. Mice were common and invaded the food bin, the bread box and, eventually, the baby's crib. In the third month of pregnancy the mother had

whooping cough and continued to cough until after the child was born. With the onset of labor, the mother was hospitalized, and delivery occurred spontaneously and without complications, after eight months of gestation, on Feb. 20, 1939. (The time at which the membranes ruptured is not known, but they were said to be intact eleven hours before delivery.) The placenta and membranes were expelled complete but were not noted to appear abnormal. The postpartum temperature fluctuated between 97 and 101.8 F. for several days and then became normal. The Kline reaction of the blood was negative on the fifth postpartum day, and the mother was discharged from the hospital in good condition on the ninth day.

Personal History and Clinical Observations.—At birth, the infant weighed 4 pounds 9 ounces (2,070 Gm.) and measured 50 cm. in length. The condition was said to be "poor," and on the second day the child was placed in an oxylator. For the first ten days of life the temperature averaged 98 F., only rarely reaching 99 F. At the age of 4 days the infant was noted to be jaundiced. A blood count at this time showed a hemoglobin concentration of 90 per cent, 4,750,000 red cells and 8,100 white cells per cubic millimeter, with 50 per cent lymphocytes, 24 per cent polymorphonuclear leukocytes, 11 per cent "stab" forms, 1 per cent myelocytes, 2 per cent eosinophils and 12 per cent monocytes. Two days later there were diffuse maculopapular rash and some generalized desquamation of the skin. The abdomen was distended, and hemorrhagic crusting was noted in the right nostril. By the beginning of the fourth week, the scaly rash on the face and body disappeared, although jaundice continued and the liver and spleen became palpable 3 fingerbreadths below the costal margin. During this period the infant gained steadily in weight. No neurologic abnormalities were noted. A few purpuric spots appeared in the skin of the neck.

Roentgenographic examination of the skull in the seventh week of life revealed many small, irregular areas of calcification bilaterally, apparently in the brain. The occipital bone was thickened, and examination of the long bones showed no evidence of syphilis, scurvy or rickets. The urine contained bile, and the icteric index was 70. Numerous examinations of the blood in the seventh to the eleventh week showed moderate anemia, the hemoglobin gradually rising from 56 to 72 per cent. The red blood cell count varied from 2,650,000 to 3,900,000 per cubic millimeter. With the improvement in the blood picture following transfusion, the white cell count fell from 17,400 to 9,000 per cubic millimeter, and small numbers of immature red blood cells, which had been present, disappeared from the smears. The differential count showed some shift to the left. Eosinophils varied from 2 to 7 per cent. Erythrocyte fragility was not increased. When the infant was about 2 months of age, the icterus had completely disappeared, although the abdomen remained distended and the liver and spleen enlarged, the spleen occupying almost the entire left half of the abdomen and extending below the iliac crest. The temperature remained normal.

The infant held his head up at 3 months, sat up at 6 months, was able to stand at 8 months and walked at 13 months of age. He never learned to talk intelligibly. At the age of 5 months it was first noted that his head was smaller than normal, measuring 13½ inches (34 cm.) in circumference, as compared with the chest, which measured 15¼ inches (38.5 cm.). The anterior fontanel was open. The microcephalus persisted, and at 11 months of age was confirmed by roentgenographic examination. Numerous intracerebral deposits of calcium, which had first been observed at the age of 7 weeks, had increased in size and number.

It was the mother's belief that the child was unable to see until he was about 8 months old, although she thought vision had improved since that time.

Physical Examination (age, 2 years).—The temperature was normal. The patient was well developed and weighed 26 pounds 6 ounces (11.9 Kg.). He was restless and uncooperative. The head was microcephalic, the suboccipitobregmatic circumference measuring 42.5 cm. and the occipitofrontal circumference 41 cm. The child was unable to speak and habitually banged his head against the crib. He was not toilet trained. Muscle strength was normal; the deep reflexes were equal on the two sides and were not hyperactive, and the Babinski reflex was not elicited. The liver and spleen were barely palpable. The skin was clear. The heart and lungs were normal.

Ophthalmologic Examination.—Vision was poor and appeared to consist only of perception of light and appreciation of moving objects within a range of about 6 feet (180 cm.). There was alternating convergent strabismus, secondary in all likelihood to the lesions in the fundi. The pupils reacted sluggishly to light and on accommodation-convergence.

Fundi: The optic nerve heads showed the gray-white pallor of secondary optic nerve atrophy. The disk margins, particularly on the right, were partly obscured by secondary glial tissue proliferation. In the right fundus there were five large, old, healed areas of chorioretinitis, horizontally arranged in the posterior third of the eyeground. The lesions were rounded, measured 2 to 6 disk diameters and had a punched-out appearance, which was accentuated by the presence of black and gray pigment. The choroid and retinal structures within the lesions were atrophic except for some deep choroidal arteries traversing their bases. Connective tissue proliferation occurred in the center of the patches and at one point formed a bridge between two large lesions inferotemporal to the disk, crossing a strip of relatively normal retina. The findings in the left fundus were in general similar to those in the right. The two largest chorioretinal lesions were 3 and 8 disk diameters in size, sharply outlined, ovoid and situated in the lower temporal quadrant. One of the smaller lesions occupied the left macular area, obliterating the fovea. All lesions showed considerable connective tissue proliferation and were heavily infiltrated with black pigment. The appearance of the various lesions remained unchanged during the observation period. The remaining retina and choroid were normal, and the media were clear.

Psychometric Examination.—The child appeared to be retarded in mental development, although in tests not requiring keen vision or the use of language his performances were normal, or a little below, for his chronologic age.

Laboratory Data.—The blood count revealed 78 per cent hemoglobin (11.4 Gm. per hundred cubic centimeters), 4,840,000 red cells and 8,900 white cells per cubic millimeter, with 44 per cent polymorphonuclear leukocytes, 49 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. Urinalysis showed no albumin, no dextrose and rare white blood cells. The Kline reaction of the blood was negative.

Roentgenographic Examination.—The bones of the skull were thicker than usual for a child of this age. The sella turcica was normal in size and shape and was not atrophic. There was no evidence of increased intracranial pressure. Many flecks of calcification were scattered throughout the cerebral hemispheres, being most abundant in the parietal and occipital areas (fig. 6). The long bones were normal. The lungs, heart and aorta showed no abnormalities. The liver and spleen were normal in size.

Attempts to Diagnose Toxoplasmosis by Laboratory Methods.—A. Cerebrospinal fluid: No fluid was available for examination.

B. Serum Neutralization Test: Examination of the patient's serum for neutralizing antibodies at the age of 2 years and 1 month yielded positive results. A test of the mother's serum gave a negative reaction (table 1).

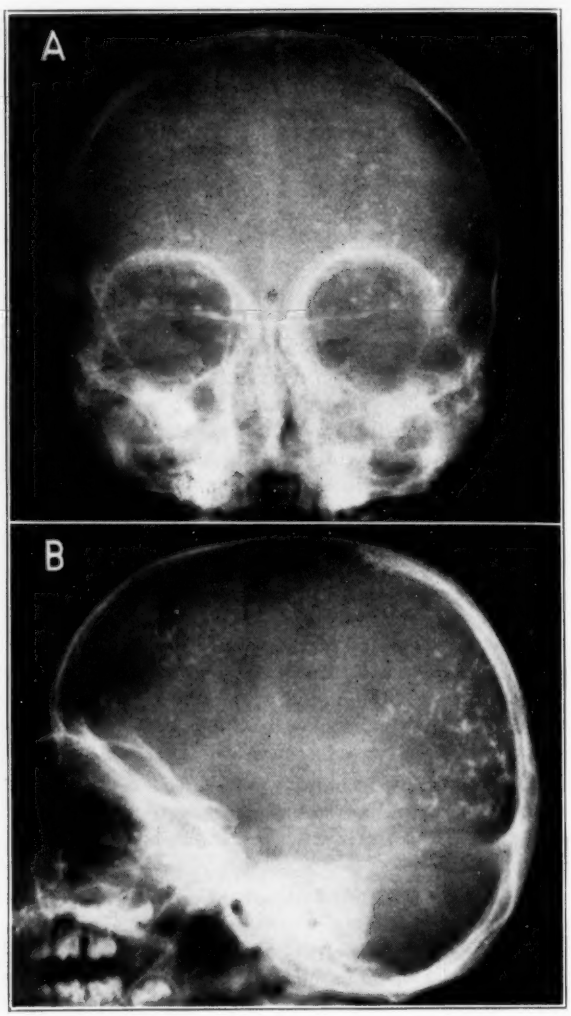

Fig. 6 (case 3; A. I.).—Roentgenograms of skull (March 20, 1941). Anteroposterior view, showing multiple, small, scattered areas of intracerebral calcification. Lateral view, with multiple, small flecks of intracerebral calcification and thickening of tables of skull associated with microcephaly.

Course.—The patient was followed two months after hospitalization, during which time his status remained unchanged. Thereafter contact with him was lost.

Summary.—A white boy of 2 years, born one month prematurely, was jaundiced on the fourth day of life and had a diffuse maculopapular rash, which lasted until the fourth week. At this time the liver and spleen became palpable. When the infant was 7 weeks old, roentgenographic examination of the skull revealed many small, irregular areas of calcification in the brain bilaterally. The icterus disappeared, and moderate anemia and leukocytosis improved after transfusion. At the age of 5 months it was observed that the head was smaller than normal, and in the ensuing months the microcephalus became more obvious. The patient did not learn to talk. At the age of 2 years ophthalmologic examination showed that vision was poor, consisting only of appreciation of moving objects and light perception. There was an alternating convergent strabismus. The fundi showed multiple focal areas of healed chorioretinitis with pigmentation. Mental development was retarded. The liver and spleen were barely palpable at this time. The multiple foci of intracerebral calcification persisted. There were no convulsions or focal neurologic signs. The patient's blood contained neutralizing antibodies to Toxoplasma, while the mother's blood proved negative.

CASE 4.—M. B., a girl 4 years of age, was admitted to the Institute of Ophthalmology and later to the Neurological Institute, with the complaint of "weakness of the left eye."

Family History.—The father, an automobile service station attendant, 35 years of age, was born in Jersey City, N. J., and, with the exception of short trips to Canada and western Pennsylvania, had never traveled. He had had one attack of severe renal colic and hematuria but was otherwise in good health. There had been some contact with rabbits raised by his father, and he occasionally ate rabbit meat. These animals were apparently normal. Boyhood contact with birds had included an Italian goldfinch, a Japanese nightingale and several young pheasants. The mother, aged 29, was born in a Pennsylvania mining town, where she had spent her girlhood. Since marriage, the parents had lived in Jersey City. Mice were only occasionally seen in the home. Household pets included only a number of cats and a canary. The patient was the second of 3 children born of this union. The first and third were entirely normal in health and mental development. Pregnancy in each instance was uncomplicated. The patient (M. B.) was born at full term after a labor of thirty-two hours, on Aug. 13, 1937. The membranes ruptured one hour before the onset of labor.

Personal History.—The infant weighed 6 pounds (2,720 Gm.) at birth and, after three months of breast feeding, was fed on a formula. Dentition began at the age of 6 months. She sat up at 7 months and walked at 14 months of age. The first attempts to talk occurred at 2 years of age. Speech development has been unsatisfactory. At present the child is more limited in speech than her younger sister, aged 3 years. The mother observed that the patient's left eye "was turned in" in early infancy, probably before the age of 2 months, and it has since remained deviated. At 2 years of age, during a paroxysm of coughing due to pertussis, a subconjunctival hemorrhage occurred in this eye. Other acute infections included measles, at 2 years, and chickenpox, at 3½ years of age. There was no history of convulsions or other neurologic abnormalities.

Physical Examination.—The patient was well developed, well nourished and cooperative. The temperature and the pulse and respiratory rates were normal. Gait and coordination were normal. There was no muscular weakness or atrophy. The deep and superficial reflexes were present and equal on the two sides. The Babinski reflex was not elicited. Sensation was normal. Cranial nerve function other than that associated with the strabismus was intact. Examination of the chest and abdomen showed no abnormalities.

Ophthalmologic Examination.—The right eye was constantly the fixing eye. There was esotropia for distance and for near fixation of 30 and 35 prism diopters, respectively. There was left microphthalmos, the left cornea measuring 7.5 mm. and the right 11 mm. in the horizontal axis. The right pupil was slightly smaller than the left. The hand loupe revealed a few remnants of pupillary membrane. Visual acuity could not be determined accurately, but small objects were recognized fairly well. Retinoscopy revealed compound hyperopic astigmatism bilaterally. The ophthalmoscope revealed a very small posterior cortical cataract and numerous vitreous opacities in the left eye.

Fundi: An old, healed, somewhat triangular chorioretinal lesion was present in the right fundus temporal to the macular region. It was heavily infiltrated with black pigment and measured about 1 disk in diameter. Some fine connective tissue bands in the retina appeared to join the apex of the lesion with the fovea. The remainder of the retina, the optic disk and the media were normal. The left optic disk showed moderate pallor. In the left fundus, a large, pigmented, ovoid chorioretinal lesion was seen in the periphery of the upper temporal quadrant. It appeared to have resulted from the coalescence of five smaller lesions, the total length being about 3 disk diameters. Occasional islands of sclera and deep choroidal arteries were observed in the base of the lesion. In addition, a very large, pale blue and grayish white area was seen in the upper nasal quadrant, the distal margins of which could not be delimited. Its surface was elevated 3 to 4 D. centrally, and its visible margin was bordered by a band of grayish black pigment. A number of small deep retinal chronic edema exudates were present in and at the margin of the lesion, and the retina adjacent to it showed slight haziness of detail, possibly indicating an active inflammatory process. However, no changes occurred in the appearance of either fundus during the observation period of many months.

Laboratory Data.—The blood count revealed 12.2 Gm. of hemoglobin per hundred cubic centimeters, 4,510,000 red cells and 5,000 white cells per cubic millimeter, with 52 per cent polymorphonuclear leukocytes, 45 lymphocytes, 1 per cent monocytes and 2 per cent eosinophils. The urine was normal. The Kline reaction of the blood was negative.

Roentgenographic Examination.—There was no evidence of increased intracranial pressure. A great many small shadows of calcium density were scattered through the cerebral hemispheres. One such streak was present in the basal ganglia, in the vicinity of the left caudate nucleus. The sella turcica, the vascular channels and the sutures appeared normal.

Psychometric Status.—Examination at 3 years and 10 months of age indicated a "low average general intelligence."

Serum Neutralization Test.—The result of this test at the age of 4 years 2 months was interpreted as positive or suggestively positive. The reaction obtained with the mother's serum was classified as doubtful or negative (table 1).

Course.—The patient's condition remained essentially unchanged during a period of six months after her discharge from the hospital. She is now 4½ years old.

Summary.—A girl aged 4 years was admitted to the hospital with internal squint of the left eye. The strabismus was first noted in early infancy, before the age of 2 months, and persisted. The child's physical status appeared to be normal, but her speech was unsatisfactory, and at the age of 4 years it was more limited than that of her sister, younger by a year. Examination of the eyes showed, in addition to the strabismus, that the left globe was smaller than the right. Bilateral focal areas of chorioretinitis with black pigmentation occurred in both fundi. Roentgenograms of the skull revealed a number of discrete shadows of calcium density within the cerebrum. The result of an examination of the patient's blood for neutralizing antibodies of Toxoplasma was classified as positive or suggestively positive. A similar test of the mother's blood yielded a doubtful or negative result.

CASE 5.—D. H., a Negro boy of 11 years, was brought to the Vanderbilt Clinic because of difficulty in vision and "fits."

Family History.—The mother was born in Barbados and lived there on a farm during her childhood. She had contact with cows, chickens, pigs, goats and wild birds, but there were no dogs, cats, canaries or mice. The house was said to be free of vermin, and there was no history of tick bites. She had eaten cooked rabbit meat infrequently. She was brought to the United States at the age of 12, lived two months in Brooklyn and then moved to Manhattan. There were no pets in the home, nor was there any severe infestation with mice. At the age of 18 years bronchopneumonia developed, necessitating hospitalization, and she was ill for a month. She married at the age of 22 years and had never left New York city thereafter. There were 8 maternal siblings, 2 brothers and sisters being alive and well. Two sets of twins had died. In Barbados, a male child had died at the age of 6 months and the twin female at the age of 22 months. The other pair had died immediately after birth, in New York city. The causes of death could not be ascertained.

The father, also born in Barbados, had come to the United States at the age of 33. He was an elevator operator and since coming to this country had always lived in New York city. He had had pneumonia at the age of 50, when he required hospitalization and was ill for six weeks.

After their marriage, the couple lived for nine years in the same home in Harlem, where all their children were born. Their apartment was moderately infested with mice but was said to be free of insect vermin. No birds had been kept as pets. During the two years before the mother bore the patient, a pet cat had become ill, refused food, became emaciated and was discarded, and a fox terrier had developed fits during the summer and was killed. Three other dogs, of indeterminate ancestry, had been kept as pets previously.

There were 4 children, of whom the patient was the last. The first boy, who had always been well, died at 12 years of age during anesthesia for removal of adenoids. The second child, a girl, died of pneumonia at 8 months, her birth and developmental history having been normal. The third child, a girl of 14, was

quite well, was normally developed and had suffered only the usual childhood infections. The mother had been well during her pregnancy. A general examination in the antenatal clinic revealed nothing abnormal, and the Wassermann reaction was negative. There was no premature rupture of the membranes.

Present Illness.—The patient was born spontaneously at term after a labor of twelve hours. He weighed 6½ pounds (3,340 Gm.) at birth, and his head was of normal size. The postpartum course of the mother was uncomplicated. The infant presented no feeding problem, had no seizures and his growth and development were normal. At 3 years of age he had a slight "asthmatic attack" with a cold.

At 4 years of age the child began to complain of pain in the eyes, and it was noticed that his left eye turned out. He was taken to the Herman Knapp Hospital, where the mother was told "that the child must have had some trouble with his eyes before birth." A general examination revealed nothing of significance. The boy began to go to public school at 5½ years of age. Examination of the eyes at 6 years of age resulted in the prescription of glasses and admission to a sight conservation class.

At the age of 7 years petit mal attacks began. These lasted about a minute on the average, varied from three to ten a day and occurred at any time during the day. While walking or in the performance of any action, the child would stop, stare, be unresponsive to the spoken word and occasionally turn partly around. This was unassociated with any abnormal movements, salivation, tongue biting or incontinence and was not preceded by an aura. There was no memory of the event. These seizures have continued to date.

The boy's eyes were reexamined at the age of 7, when it was noted that he had an old central chorioretinitis bilaterally. In an intelligence test at this time he was graded as of average intelligence for his age, or only slightly below it. He continued in the sight conservation class but began to have increasing difficulty with his school work. At the age of 10 he was referred to the pediatric epilepsy clinic, where he was followed as a case of idiopathic petit mal. The seizures were not affected by phenobarbital but were considerably reduced by dilantin. Examination at this time revealed a normal blood pressure and temperature. There was an enlarged lymph node in the left axilla. Because of the chorioretinitis, the possibility of syphilis was raised, but a Kline test gave negative results. A Mantoux test gave a positive reaction, and a roentgenogram of the chest revealed healed apical tuberculosis. A blood count showed a hemoglobin content of 14.5 Gm. per hundred cubic centimeters and 6,200 white cells per cubic centimeter, with 55 per cent polymorphonuclear leukocytes, 35 per cent lymphocytes, 7 per cent monocytes and 3 per cent eosinophils. The red blood cells were normal, no sickling being observed. Urinalysis revealed nothing abnormal. An electroencephalogram was indicative of petit mal. He was seen in the allergy clinic because of the "asthmatic attacks" previously noted, which were associated with colds occurring in the winter and autumn, and the diagnosis of allergic asthma was made. An intelligence test, repeated when he was 10 years 8 months old, revealed an intelligence quotient of 72 per cent, or a developmental level of 7 years 8 months. His school work had deteriorated correspondingly, and he had been left back in a 4 B class. He preferred to play with children 5 or 6 years old. At this time the patient seemed robust but was shy and responded hesitatingly. General physical and neurologic examinations revealed nothing significant except for the ophthalmologic changes and the evidence of mental retardation.

Ophthalmologic Examination.—Externally no abnormalities, congenital or acquired, were seen except for moderate external strabismus of the left eye to approximately 15 degrees. This was probably secondary to very poor vision in this eye, capable only of counting fingers at 6 inches (15 cm.), as compared with vision in the right eye, which was 20/100.

Fundi: The changes were essentially similar in the two eyes. In each fundus, centrally, was a large ovoid area of healed, old chorioretinitis. The diameter of each fundus was approximately 3 disk diameters, and the long axis was horizontal. There was some chorioretinal atrophy, with much filling in by irregularly deposited, deep and superficial, black and brownish black pigment. The borders of the lesions were sharply outlined by pigment, and their nasal margins were a little less than 1 disk diameter from the margin of the temporal disk. A few narrow choroidal arteries were seen in the bases of the lesions. Peripheral and temporal to each lesion there were several identical, but much smaller, lesions, measuring less than 1 disk diameter. The disks were somewhat pale temporally, but there was no true atrophy. The remainder of each retina and choroid was normal. The media were clear.

Roentgenographic Tests.—A faint area of calcification occurred in the region of the head of the right caudate nucleus. There was no evidence of increased intracranial pressure. The roentgenograms of the chest showed two small lesions of calcium density in the upper lobe of the right lung. There was an area of increased density above the left hilus, which virtually disappeared in the course of several months.

Serum Neutralization Test.—Neutralizing antibodies to Toxoplasma were demonstrated in the serum of the patient at the age of 11 years 3 months, and in that of his mother (table 1).

Course.—The boy has had some reduction in the number of seizures through the use of dilantin. There has been no further change in his condition during the past few months. He is now 11½ years of age.

Summary.—A Negro boy of 11 years had, in his mother's opinion, been normal until the age of 4 years, when there developed external strabismus and pain in the left eye. An ophthalmologist expressed the opinion that the ocular lesions were of prenatal origin. At the age of 7 the boy became subject to frequent petit mal attacks, which recurred at short intervals thereafter. Reexamination of the eyes revealed the presence of an old central chorioretinitis bilaterally. An intelligence test at 10 years 8 months showed subnormal intelligence. The general and neurologic examinations showed nothing abnormal except for external strabismus in the left eye and reduced vision in both eyes, particularly the left. Each fundus showed one large central and several smaller, sharply demarcated, chorioretinal lesions. A roentgenogram of the head revealed calcification in the right basal ganglia, and electroencephalograms disclosed changes associated with the petit mal attacks. The serum of this patient and that of his mother contained neutralizing antibodies to Toxoplasma.

CASE 6.—C. J., a white boy aged 7½ years, was brought to the Vanderbilt Clinic because of "trouble with his eyes since birth."

Family History.—The mother, 29 years of age, was born in New York city and had lived there all her life except for an eleven day trip to Quebec recently. She had had "rheumatism" as a child and had suffered from joint pains at times since. At the age of 19 years, she had owned a monkey for a few months. This animal had been well. A canary was in her parents' possession for sixteen years and died of old age. There were no other animal contacts, and her parental home was said to have been free of vermin. There was no history of tick bites.

The father, 28 years of age, was born in Denmark and came to the United States at 15 years of age. The couple had been married about eight and a half years ago. They had lived in a number of relatively modest homes in New York city. These were said not to have been infested by mice or other vermin. The family had had two dogs, which had been well.

The patient was the first child. There had been a stillbirth four years ago. The mother had been well during her pregnancy with the patient. According to the mother's story, there had been leakage of amniotic fluid for five days before labor began.

Personal History and Clinical Observations.—The birth of the patient was spontaneous, at full term, after an eight hour labor. The umbilical cord was found about the neck. The infant was placed on a regimen of artificial feedings at once because of deficient maternal lactation, but gained weight and grew normally. He sat up at 7 months and began to walk at 13 months of age. Although he spoke a few words at 2 years, he did not learn to speak fully until the age of 4.

At 3 months of age the mother noticed that the infant did not follow objects with his eyes and that at times there was "twitching" and occasionally turning in of the eyes, the latter being more noticeable on the right. Her physician claimed to have noted abnormal ocular movements soon after birth. The eyes were examined at a number of hospitals during the first year. The mother was told that one eye was nearly blind and the sight of the other very weak and that the condition was incurable.

At 18 months of age the boy had his first seizure, which consisted of tonic contractions of the muscles of all four extremities and unconsciousness for fifteen to twenty minutes. The next seizure occurred at 2 years of age. The boy was hospitalized and a spinal puncture done, but no diagnosis was made. Encephalographic examination at 3½ years of age revealed incompletely filled ventricles, which were thought to be of normal contour. Convulsions recurred each month thereafter for six months. They now included clonic movements, salivation, tongue biting and at times incontinence of urine and feces, and some aura must have preceded them, for the child would lie down before the attack began. Thereafter the seizures became less frequent, occurring every three months at first and finally not recurring for a year and a half. The boy started school at 6½ years of age, but his inability to keep up with the work in the sight conservation class necessitated transfer to a school for the blind.

Physical Examination.—The child was well developed and nourished. He walked on a slightly widened base and placed his feet inaccurately. He tended to lose his balance and was unable to stand steadily on either foot. There were a fine tremor of the arms, more noticeable on the left side than on the right, and some dysmetria on the left. There were occasional involuntary movements of the hands.

Ophthalmologic Examination.—Visual acuity was greatly reduced. There was bilateral microphthalmos, the corneas of both eyes measuring a scant 10.5 mm. in the horizontal axis. There was searching and rotary nystagmus, with inability to fix with either eye. The right eye deviated inward about 25 degrees.

Fundi: Obliterating the macular region of each eye was a large, round, diffusely pigmented area of old, healed chorioretinitis about 4 disk diameters in size. Islands of yellowish white sclera were visible through these lesions, which were diffusely infiltrated and marginally outlined by heavy black pigment. The surface was rendered irregular and elevated in places as a result of connective tissue proliferation. Some narrow choroidal arteries were visible in the bases of the lesions. Peripheral to the main lesion in each eye was a satellite group of eight to ten similar, smaller lesions, less than 0.5 disk diameter in size, the greater number of which were located about the horizontal axis. There were pronounced pallor and atrophy of the optic nerve heads. The media were clear.

Other Examinations.—Roentgenograms of the skull were normal in all respects. The electroencephalogram was diffusely pathologic, with suggestive evidence of a midline parieto-occipital focus and convulsive patterns.

On psychometric examination the boy appeared to be of average general intelligence and somewhat retarded in manual efficiency.

Serum Neutralization Test.—Examination of the patient's serum for neutralizing antibodies at the age of 7 years 7 months yielded a suggestively positive result (table 1).

Course.—The patient's condition has remained unchanged during a six month period of observation. He is now 8 years old.

Summary.—A white boy aged 7½ years was brought to the clinic for "trouble with his eyes." At 3 months of age the mother had noticed that the infant did not follow objects with his eyes, that he showed "twitching of the eyes" and that there was an occasional internal squint, especially on the right. In the first year one eye was nearly blind and sight in the other was poor. At 18 months of age the boy had his first convulsive seizure, which was generalized and accompanied by unconsciousness. Further convulsions occurred at varying intervals during the following years. On neurologic examination at 7½ years of age, the patient was found to walk on a slightly widened base and tended to lose his balance. There were a fine tremor of the arms and some dysmetria on the left. The eyes showed a wandering horizontal and rotary nystagmus. Central areas of old chorioretinitis were present bilaterally, with smaller peripheral lesions. Roentgenograms of the skull were normal. The electroencephalogram was diffusely pathologic. The test for neutralizing antibodies in the patient's blood proved suggestively positive.

SEROLOGIC TESTS FOR TOXOPLASMOSIS

The difficulty of detecting the parasite, Toxoplasma, in the blood or the spinal fluid in suspected cases of toxoplasmosis by direct examination or by animal inoculation makes it desirable to confirm the diagnosis, if possible, by serologic methods. The strong resistance to

reinoculation which develops in experimental animals recovering from a nonlethal toxoplasmic infection suggests that antibodies may occur in the blood of such animals. An early experiment was that of Sarrailhé (1914),[7] who inoculated mice intraperitoneally with mixtures of Toxoplasma and serum. This author observed no protective activity with either normal serum (human, monkey, rat) or convalescent serum (dog, mouse). Levaditi and his co-workers (1929),[8] also, could not demonstrate any tendency of convalescent rabbit serum to "neutralize" Toxoplasma in vitro and concluded that immunity in the rabbit was essentially of a cellular nature. Nicolau and Ravelo (1937),[9] on the other hand, developed a complement fixation test for animal toxoplasmosis and found apparently specific antibodies in the serum and in organ extracts of rabbits and various other animal species infected with Toxoplasma. Sabin and Olitsky (1937) [10] applied the principle of the neutralization test, currently used in filtrable virus studies, to animal toxoplasmosis. By inoculating rabbits intracutaneously with mixtures of serum and suspensions of tissues infected with Toxoplasma, protective activity was demonstrated by the serum of monkeys recovering from nonlethal toxoplasmosis, and recently by serum obtained post mortem from a child found at autopsy to have toxoplasmosis.[3] The serum in each of the 6 proved or suspected cases of toxoplasmic encephalomyelitis reported in this paper has provided evidence of antitoxoplasmic activity in one or more trials by the skin protection test method of these investigators. Inasmuch as the technic of performing the test has not been recorded in detail, an outline of the procedure as used in this laboratory is given here. The limitations of the method will be discussed later.

Technic of Serum Neutralization Test for Toxoplasmosis.—Principle: Intracutaneous inoculation of the rabbit with a suspension of tissue infected with Toxoplasma is followed by the development of a localized inflammatory lesion at the site of injection. Inhibition of the development of the cutaneous lesion, when suitable dilutions of Toxoplasma-infected tissue are mixed with serum in vitro prior to inoculation, is an indication of antitoxoplasmic activity of the serum. The lesions are compared in size and appearance with those developing after the simultaneous inoculation of the same animal with mixtures of Toxoplasma and control serum, and with Toxoplasma in the absence of serum.

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7. Sarrailhé, A.: Notes sur la toxoplasmose expérimentale, Bull. Soc. path. exot. **7**:232, 1914.

8. Levaditi, C.; Sanchis-Bayarri, V.; Lépine, P., and Schoen, R.: Etude sur l'encéphalo-myélite provoquée par le Toxoplasma cuniculi: II, Ann. Inst. Pasteur **43**:1063, 1929.

9. Nicolau, S., and Ravelo, A.: La réaction de fixation du complément dans le sérum et dans des extraits d'organes d'animaux atteints de toxoplasmose expérimentale, Bull. Soc. path. exot. **30**:855-859, 1937.

10. Sabin, A. B., and Olitsky, P. K.: Toxoplasma and Obligate Intracellular Parasitism, Science **85**:336-338, 1937.

Serum: Blood is obtained by venipuncture under sterile precautions from a patient suspected of having the disease. After coagulation is complete, the serum is separated by centrifugation and stored in the refrigerator in sterile sealed tubes without the addition of preservative. An attempt is made to use relatively fresh serum, i. e., within a week of its removal. Serum older than three weeks has not been used in the present series of tests. If it proves necessary to delay the performance of the test beyond this period, the serum may be frozen and desiccated by the lyophile method for later use. The dried serum is rehydrated to its original volume by the addition of sterile distilled water shortly before use.

Control Serum: Tests on two control serums are run in parallel with each serum tested. Such serum has been obtained indiscriminately from either presumably normal persons or, more commonly, from persons with various neurologic or non-neurologic disorders. However, since the final readings are essentially comparative, care is taken as far as possible to choose as the source of the control serum persons of the same age and sex as the patient under investigation and to obtain the blood on the same day. It is inadvisable in a given test to use serums which have been kept for dissimilar periods following the withdrawal of the blood.

Source of Toxoplasma and Preparation of Suspensions: Mouse brain infected with the human B D [2] or L M [1c] strain of Toxoplasma is the source of the parasite. Several lines of infected mice are constantly maintained in the laboratory by regular serial passage. The brains of 2 mice which are ill or have recently died of the infection after intracerebral inoculation (usually on the fifth or sixth day) are removed aseptically, weighed, ground without abrasive and suspended in nine times their weight of sterile buffered isotonic physiologic salt solution. (A satisfactory solution of this type is that of Simms,[11] with a p_H of about 7.4. Simple unbuffered isotonic solution of sodium chloride as a diluent is usually unsatisfactory.) The suspension of infected brain tissue is centrifuged at very low speed for one-half minute to deposit the coarser particles, and the cloudy supernatant fluid is pipetted off for use in the test. Rapid or prolonged centrifugation is to be avoided. The tissue suspension is designated a "1 : 10 dilution of Toxoplasma," and from it a series of higher dilutions is prepared by addition of appropriate amounts of buffer solution. In practice, preliminary dilutions of (1) 1 : 10, (2) 1 : 50, (3) 1 : 100, (4) 1 : 200, (5) 1 : 400 and (6) 1 : 800 have been found convenient. These suspensions are freshly prepared at the beginning of each test.

Rabbits: Two albino rabbits, 4 to 6 months of age, are used in each test. The performance of the test in duplicate is not essential, but is advisable, since an occasional rabbit dies of disseminated toxoplasmosis before the readings have been completed or fails to manifest adequate lesions because of "spontaneous" immunity to Toxoplasma. The entire back of each animal is prepared by shaving with an electric clipper, and the available area of skin is squared into the desired number of injection sites by painting on lines of dye (gentian violet). Four longitudinal columns (A, B, C and D), each subdivided into 6 squares (for the six dilutions of mixed infected tissue and serum), a total of 24 injection sites, are ordinarily used for each rabbit.

Glassware: The serum-Toxoplasma mixtures are prepared in sterile, rubber-stoppered Wassermann tubes. Tubes about 6 cm. in length are more conveniently entered by the syringe than the standard 10 cm. tube. Sterile 1 cc. pipets graduated in hundredths are used for measuring and transferring the desired quantities of serum and tissue suspensions. Inoculations are made with 1 cc. tuberculin

11. Simms, H., cited by Sanders, M.: Studies on the Cultivation of the Virus of Lymphogranuloma Venereum, J. Exper. Med. **71**:113-128, 1940.

syringes equipped with sharp 27 gage, ½ inch (1.27 cm.) needles. At least as many syringes and needles should be available as there are inoculations to be made. They are sterilized and assembled before beginning the test.

Procedure: Four sets, A, B, C and D, of 6 tubes each are set up. Four-tenths cubic centimeter of the serum to be tested is pipetted into each tube of set A; 0.4 cc. of control serum 1 into each tube of set B, and 0.4 cc. of control serum 2 into each tube of set D. In place of serum each tube of set C receives 0.4 cc. of the buffered salt solution diluent. To the first tube of each of the four sets, 0.4 cc. of Toxoplasma suspension 1 (dilution 1:10) is now added by pipet; to the second tube of each set, 0.4 cc. of Toxoplasma suspension 2 (dilution 1:50), and so on until the entire set of mixtures is completed, as follows:

	Final Dilution of Infected Brain Tissue					
Set	1	2	3	4	5	6
A Test serum plus Toxoplasma...	1:20	1:100	1:200	1:400	1:800	1:1,600
B Control serum 1 plus Toxoplasma	1:20	1:100	1:200	1:400	1:800	1:1,600
C Buffer solution plus Toxoplasma	1:20	1:100	1:200	1:400	1:800	1:1,600
D Control serum 2 plus Toxoplasma	1:20	1:100	1:200	1:400	1:800	1:1,600

The entire rack of tubes is thoroughly shaken to insure complete mixing, and the mixtures are allowed to stand at room temperature until the inoculations are performed. An in vitro contact time of two to two and one-half hours has proved satisfactory. Since considerable time is required to load the syringes with the serum-Toxoplasma mixtures, this operation is begun about one-half hour before the time fixed on for starting the inoculations. The loaded syringes are laid out in orderly fashion, the attached needles being protected by sterile gauze. The rabbits, prepared as already described, are kept lightly anesthetized with ether during the inoculations. Each mixture is injected intracutaneously in a volume of 0.25 cc. at the site previously marked out for it. Inoculations are made in the same order used in preparing the mixtures, i. e., dilution 1: A → B → C → D; dilution 2: A → B → C → D, etc., both rabbits being inoculated from the same syringe. In this way, the in vitro contact period in any given dilution is almost identical for the test serum and its three controls. However, the higher dilutions may have slightly longer contact periods than the lower, because of the time required for making the inoculations.

Readings: The animals are observed for twelve to fourteen days, occasionally longer, and a daily record is made of the appearance and size of all lesions. The large wheal raised at each injection site subsides within twenty-four hours. It is often followed by a nonspecific, diffuse erythema, due to the inoculation of foreign serum. In most cases this erythema disappears in forty-eight to seventy-two hours. The specific lesion due to Toxoplasma becomes apparent two to four days after inoculation as a colorless or pinkish papule which increases in size, deepens in color and becomes more elevated, usually reaching its maximum size in seven to ten days. The size of each lesion is recorded in millimeters by measuring two diameters, one of these being the largest diameter, the other being at right angles to it. At times, the limits of a lesion are too poorly defined to permit of accurate measurement, in which case the reading is recorded with a question mark to indicate its questionable accuracy. While the nodular lesion is developing, its central portion, in the more severe lesions, usually becomes discolored and necrotic and appears as a brown crust, the size of which is also recorded in millimeters. The method of keeping the records will be clear from the following sample partial protocol.

Dilution of Toxoplasma	Date	Rabbit 491, Inoculated 11/6/41			
		A Serum of Patient D. H. (Case 5)	B Control Serum 1	C Buffer Control	D Control Serum 2
	11/ 7/41	Large wheal (reaction to foreign serum)	Large wheal (reaction to foreign serum)	—	Large wheal (reaction to foreign serum)
	11/ 8/41	Fading serum reaction; pale pink papule, 6 by 6	Fading serum reaction; pale pink papule, 8 by 7	Pink papule, 9 by 8	Fading serum reaction; pale pink papule, 7 by 6
	11/ 9/41	Pink papule, 7 by 7	Pink papule, 9.5 by 7, with central pallor	Pink papule, 10.5 by 9	Pink papule, 9 by 8
	11/10/41	Pink papule, 8.5 by 7, with central pallor	Pink papule, 10.5 by 9.5, with central pallor	Pink papule, 13 by 12, with slight central pallor	Pink papule, 9 by 8, with central pallor
	11/11/41	Pink papule, 9.5 by 8.5, with central pallor	Pink papule, 11 by 10, central brown necrosis, 2.5 by 1.5	Pink papule, 13 by 11, central pallor (early necrosis ?)	Pink papule, 11 by 8.5, with central pallor
1:20	11/12/41	Pink papule, 9 by 9, with central pallor	Pink papule, 11 by 10.5; central brown necrosis, 4 by 4	Pink papule, 13 by 11; central brown early necrosis, 3.5 by 1.5	Pink papule, 10.5 by 9.5; central, yellowish brown early necrosis, 3 by 2.5
	11/13/41	Pink papule, 10 by 9, with central yellowish pallor	Pink papule, 12 by 11; central brown crust, 5 by 4	Pink papule, 12 by 11; central brown crust, 4.5 by 2.5	Pink papule, 11 by 9; central pallor and early necrosis, 2.5 by 1.5
	11/14/41	Pink papule, 9 by 8.5; yellowish brown central crust, 3 by 2.5	Pink papule, 11.5 by 10.5; central brown crust, 5 by 4	Pink papule, 14 by 12; central brown crust, 5 by 3.5	Pink papule, 12 by 9; central brown crust, 3 by 2
	11/15/41	Pink papule, 9 by 9; central brown necrosis, 3 by 2	Pink papule, 11 by 10.5; central brown crust, 6 by 5	Pink papule, 14 by 13; central brown crust, 6 by 4	Pink papule, 11.5 by 9; central brown necrosis, 3 by 2
	11/18/41	Pink papule, 9 by 9; central brown crust, 4 by 3	Pink papule, 11 by 10; central brown crust, 6.5 by 5.5	Pink papule, 14 by 11; central brown crust, 6 by 4.5	Pink papule, 12 by 10.5; central brown crust, 5 by 3
	11/24/51	Brown crust, 4 by 3.5	Brown crust, 5.5 by 5	Brown crust, 6 by 4.5	Brown crust, 5 by 3
	11/ 7/41	Large wheal (reaction to foreign serum)	Large wheal (reaction to foreign serum)	—	Large wheal (reaction to foreign serum)
	11/ 8/41	Fading serum reaction	Fading serum reaction	Pale pink papule, 4 by 4	Fading serum reaction
	11/ 9/41	Small, colorless papule	Small, pale elevation	Pink papule, 7 by 6	Pink papule, 8.5 by 7
	11/10/41	Indefinite pale papule, 4 by 4	Pink papule, 10 by 10	Pink papule, 9 by 9	Pink papule, 10 by 9.5
	11/11/41	Pale pink papule, 4 by 4	Pink papule, 11 by 10; slight central yellowish discoloration	Pink papule, 10 by 9.5; slight central yellowish pallor	Pink papule, 9 by 8.5
1:100	11/12/41	Pale pink papule, 5 by 4.5	Pink papule, 10 by 10; central brown necrosis, 2.5 by 1	Pink papule, 10.5 by 10.5	Pink papule, 10 by 9.5
	11/13/41	Pale pink papule, 6 by 6	Pink papule, 12 by 11; central brown necrosis, 4 by 3	Pink papule, 11.5 by 11.5; slight central crusting, 3.5 by 3 (?)	Pink papule, 11 by 11; slight central pallor
	11/14/41	Pale pink papule, 6 by 5	Pink papule, 13 by 12; central brown crust, 4 by 3.5	Pink papule, 12.5 by 10; central brown crust, 4.5 by 3.5 (?)	Pink papule, 12 by 11.5; slight central crusting, 3.5 by 2.5
	11/15/41	Pale pink papule, 6 by 5.5; no necrosis	Pink papule, 12.5 by 12; central brown crust, 5 by 4	Pink papule, 12 by 10; central brown crust, 6 by 5	Pink papule, 11.5 by 11; central brown crust, 3 by 2.5
	11/18/41	Pale pink papule, 5 by 5; no necrosis	Subsiding pink papule, 10.5 by 9; central brown crust, 5.5 by 5	Pink papule, 11 by 10; central brown crust, 6 by 4.5	Pink papule, 11.5 by 9.5; central brown crust, 3.5 by 2.5
	11/24/41	Pale area	Brown crust, 6 by 4	Brown crust, 6 by 4	Brown crust, 4.5 by 3.5

Dilution of Toxoplasma	Date	Rabbit 491, Inoculated 11/6/41			
		A Serum of Patient D. M. (Case 5)	B Control Serum 1	C Buffer Control	D Control Serum 2
	11/ 7/41	Large wheal (reaction to foreign serum)	Large wheal (reaction to foreign serum)	—	Large wheal (reaction to foreign serum)
	11/ 8/41	Fading serum reaction	Fading serum reaction	—	Fading serum reaction
	11/ 9/41	—	—	Pale pink papule, 6 by 5	Indefinite pale pink papule, 6 by 5 (?)
	11/10/41	Indefinite pale elevation, 4 by 3.5	Pale pink papule, 8 by 8	Pink papule, 9 by 8	Pink papule, 9 by 9
	11/11/41	Colorless papule, 4.5 by 3.5	Pale pink papule, 8 by 8	Pink papule, 9 by 9	Pink papule, 9 by 8.5
	11/12/41	Pale pink papule, 6 by 4	Pink papule, 8 by 8	Pink papule, 10 by 9.5	Pink papule, 10 by 9.5
1:200	11/13/41	Pale pink papule, 5 by 5	Pink papule, 10 by 8; slight central yellowish crusting	Pink papule, 10 by 10	Pink papule, 12 by 11; central reddish necrosis, 3 by 2.5
	11/14/41	Pale pink papule, 5 by 5	Pale pink papule, 10.5 by 10; central yellowish brown crusting, 4.5 by 4.5	Pink papule, 10 by 10; central brown crusting, 5 by 3.5	Pink papule, 11 by 10; central brown crust, 4 by 3.5
	11/15/41	Pale pink papule, 5 by 5; no necrosis	Pink papule, 9 by 8.5; central brown crust, 5 by 4.5	Pink papule, 11.5 by 11; central brown crust, 5 by 4.5	Pink papule, 10 by 9; central brown crust, 4 by 4
	11/18/41	Pale pink papule, 5 by 5; no necrosis	Subsiding pink papule, 9 by ?; central brown crust, 5.5 by 4	Pink papule, 11 by 10; central brown crust, 5 by 4	Subsiding pink papule, 9 by 9 (?); central brown crust, 5 by 4
	11/24/41	Pale area	Brown crust, 5 by 4	Brown crust, 4.5 by 4	Brown crust, 5 by 5
	11/ 7/41	Large wheal (reaction to foreign serum)	Large wheal (reaction to foreign serum)	—	Large wheal (reaction to foreign serum)
	11/ 8/41	Fading serum reaction	Fading serum reaction	—	Fading serum reaction
	11/ 9/41	—	—	—	Faint residual serum reaction
	11/10/41	—	Pale pink papule, 6 by 5 (?)	Pale pink papule, 7 by 6	Pale pink papule, 8 by 7.5
	11/11/41	—	Indefinite pale pink papule, 6.5 by 6 (?)	Pink papule, 7 by 6	Pink papule, 7.5 by 6
	11/12/41	—	Pale pink papule, 7 by 7	Pink papule, 7.5 by 6.5	Pink papule, 9 by 8
1:400	11/13/41	Indefinite pale area	Pink papule, 9 by 8.5	Pink papule, 8 by 7	Pink papule, 8.5 by 8
	11/14/41	Indefinite pale area	Pale pink papule, 9 by 8	Pale pink papule, 8 by 8	Pale pink papule, 8 by 8; central brownish crust, 4 by 2.5
	11/15/41	Pale elevation, 3 by 2 (?)	Pale pink papule, 10.5 by 9; central yellowish brown crust, 2.5 by 2	Pale pink papule, 9 by 7; several small brownish crusts, 1 by 1	Pale pink papule, 11 by 8.5; central brown crust, 5 by 4.5
	11/18/41	Small, colorless area	Pale pink papule, 10 by 9 (?); central brownish crust, 3.5 by 2.5	Pale pink papule, 9 by 7.5; several small central brown crusts, 1 by 1	Subsiding pale pink papule, 9 by 8; central brown crust, 5 by 4.5
	11/24/41	—	Brown crust, 3 by 2	Pale area (crusts separating)	Brown crust, 4.5 by 9
1:800 etc.					
1:1,600 etc.					

Interpretation of the Test and Limitations of the Method.—A comparison of the size, depth of color and occurrence and severity of central necrosis of the papules which develop at the various sites of inoculation is the basis for conclusions as to the result of the test. A review of the readings made over the total period of observation, or at the time when the lesions have reached their maximum development, has led to a diagnosis of a positive or a suggestively positive result when the lesions with the test serum are consistently less severe than those with each of the three controls. When differences between the lesions with the test serum and those with the controls are slight or absent, the result is considered doubtful or negative. At times, the higher dilutions are more favorable for revealing such differences. Thus, in the accompanying protocol the papules developing in the presence of the test serum (D. H.; case 5) are consistently smaller than those with the controls, but this is less apparent in the 1:20 dilution than in the 1:100 and 1:200 dilutions. The same is true of the tendency toward central necrosis, which in the example cited is only slightly less evident with the test serum than with the controls in the 1:20 dilution. However, in the 1:100 and in the higher dilutions necrosis is completely absent in the lesions with the test serum while it is well marked in the control lesions. The point at which the difference in response is most apparent depends on the degree of infectivity of the Toxoplasma-infected material in a given test and on the variable antibody content of the serum. Nevertheless, in most instances, if differences are present, they are noted in all, or almost all, dilutions in varying degree. In the highest dilutions the test serum lesions may be completely inhibited, while the control lesions continue to appear. Thus, in the example cited, test serum lesions virtually disappeared at the 1:400 dilution and beyond, although control lesions developed. In estimating the results of the tests, the term "positive" (+) is used if the test serum lesions and the central necrosis are in general one-half or less the size of the control lesions and are entirely inhibited in the higher dilutions of Toxoplasma at which control lesions still appear. A distinct, but less marked, difference is termed "suggestively positive" (±), and when the contrast is minor or absent, the result is indicated as doubtful or negative (—).

From the preceding discussion, it will be clear that the test is in no sense absolute and that categoric criteria for what constitutes a positive result cannot be formulated. The use of infected mouse brain suspensions in which the numbers of parasites no doubt vary, does not permit the establishment of a standard unit of infective material constant from test to test. The variability with which different rabbits react to the same infective material prevents quantitation of the results, although the relative responses are generally similar from rabbit to rabbit. These two factors render invalid a direct comparison in quantitative terms of the lesions in one test with those produced by the same dilutions of infected brain tissue and serum in another test. Thus, the comparative antitoxoplasmic activity of one serum with respect to another can be estimated only in the same animal. Furthermore, in any given animal, the three control mixtures do not always result in equally well developed lesions, particularly in the higher dilutions. One control serum may be associated with more pronounced lesions than the other, and both may be less well developed than those resulting from the mixtures in which buffer solution has been substituted for serum. These irregularities in the results make it of doubtful value to attempt to express the neutralizing power of the serum in terms of skin protective units. Such irregular responses make it necessary in any given test to use as controls not only suspensions of Toxoplasma in buffer solution alone, but those containing "normal" serum as well, since the specificity of the protective

activity of the test serum might otherwise be questioned. The variability of different control serums may depend on nonspecific protective activity, or may be related to a more or less widespread subclinical or healed toxoplasmosis in the population, with the development of specific antibodies in some persons. Information as to the latter point must await the development of a more specific serologic test for toxoplasmosis. With respect to the variability of "normal" control serums, our experience differs from that of Sabin,[3] who observed no neutralization of any kind with fifteen serums of various sorts used as controls.

The results of the test are tabulated in table 1.

TABLE 1.—*Results of Neutralization Tests*

Authors' Series	Source of Serum	Age of Patient at Time of Test	Result *	Parent Whose Serum Was Tested	Age of Child at Time of Parent's Serum Test	Result *
2 (Cases diagnosed clinically)	Case 1 (P. D.)	3 yr. 10 mo. 3 yr. 10½ mo. 3 yr. 11 mo.	+ ± +	Mother Father	4 yr. 4 yr. 7 mo.	− −
	Case 2 (J. P.)	8 mo.	+	Mother	8 mo.	±
	Case 3 (A. I.)	2 yr. 1 mo.	+	Mother	2 yr. 2 mo.	−
	Case 4 (M. B.)	4 yr. 2 mo.	+ or ±	Mother	4 yr. 3½ mo.	−
	Case 5 (D. H.)	11 yr. 3 mo.	+	Mother	10 yr. 11½ mo.	+
	Case 6 (C. J.)	7 yr. 7 mo.	±			
1 (Cases diagnosed at autopsy)	Case 3 [1c] (L. M.)	Patient's serum not tested; toxoplasmosis not diagnosed until autopsy		Mother	16 mo.†	+
	Case 4 [1c] (B. R.)	Patient's serum not tested; toxoplasmosis not diagnosed until autopsy		Mother	3 wk.† 8½ mo.†	+ +
	Case 5 [1c] (A. M. T.)	Patient's serum not tested; toxoplasmosis not diagnosed until autopsy		Mother	6½ wk.† 10 mo.†	± ±

* + indicates a positive reaction; ± a suggestively positive reaction, and −, a doubtful or negative reaction.

† Values for cases 3, 4 and 5 in this series indicate the time after the patient's birth at which the parent's serum was tested.

COMMENT

In the 6 cases reported here certain fundamental similarities in the clinical picture suggested a common etiologic factor. They presented evidence of disease of the central nervous system beginning early in life, often during infancy. In all cases chorioretinitis was noted early, and was often the presenting symptom. Roentgenographic evidence of intracerebral calcification was present in all but 1 case. A comparison of these findings with those in a series of cases proved by autopsy to be instances of toxoplasmic encephalomyelitis led to the suspicion that they, too, were instances of the same disease. An attempt was then made to establish the diagnosis by serologic means, and in some instances

by the inoculation of laboratory animals with blood and cerebrospinal fluid in an effort to isolate the causative micro-organism. In each of the cases here reported, the neutralization test previously described proved positive. The significance and limitations of this test have already been discussed. In 2 cases the serum of the mothers as well proved to be positive, and the further implications of these results, other than those having to do with diagnosis, will be referred to later. In 1 case organisms, which were identified as Toxoplasma, were discovered in ventricular fluid removed in the process of ventriculography. In another case inoculation of mice with ventricular fluid resulted in the production of toxoplasmosis in 1 animal which could be transmitted serially. Taken together, these findings led us to believe that we were dealing with a group of patients who had acquired toxoplasmosis early in life, possibly in utero, affecting chiefly the central nervous system and the eyes. Analysis of the clinical histories and the results of examination in these cases, as well as in those in which autopsy was performed, yields a well rounded clinical picture which permits of identification of instances of infantile toxoplasmic encephalomyelitis during life. The following analysis includes 5 cases in which autopsy was done,[1] the 6 clinical cases described here and 4 instances from the literature.[12] In the last 4 cases the condition had been variously diagnosed by the authors on the basis of autopsy observations and was later reclassified by us as toxoplasmosis.[13] A case of infantile infection with Toxoplasma discovered at autopsy without lesions or symptoms referable to the parasite [4a] is not included in the following summary.

Clinical Features (table 2).—In the 15 cases referred to in the preceding paragraph 8 patients were females and 7 were males. Ten

12. (*a*) Jankû, J.: Parasites in Coloboma of Macula, Časop. lék. česk. **62**: 1021-1027, 1054-1059, 1081-1085, 1111-1115 and 1138-1143, 1923. (*b*) Magarinos Torres, C.: Sur une nouvelle maladie de l'homme, caracterisée par la présence d'un parasite intracellulaire, très proche du Toxoplasma et de l'Encéphalitozoon, dans le tissu musculaire cardiaque, les muscles du squelette, le tissu cellulaire sous-cutané et le tissu nerveux, Compt. rend. Soc. de biol. **97**:1778-1781, 1928; Morphologie d'un nouveau parasite de l'homme, Encéphalitozoon chagasi, n. sp., observé dans un cas de méningo-encéphalo-myélite, congénitale avec myosite et myocardite, ibid. **97**: 1787-1790, 1928; Affinités de l'Encéphalitozoon chagasi, agent étiologique d'une méningoencéphalo-myélite congénitale avec myocardite et myosite chez l'homme, ibid. **97**:1797-1799, 1927. (*c*) Richter, R.: Meningo-Encephalomyelitis Neonatorum: Anatomic Report of a Case, Arch. Neurol. & Psychiat. **36**:1085-1100 (Nov.) 1936. (*d*) de Lange, C.: Klinische und pathologisch-anatomische Mitteilungen über Hydrocephalus chronicus congenitus und acquisitus, Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:433-500, 1929.

13. Wolf, A., and Cowen, D.: Toxoplasmic Encephalomyelitis, in Blumer, G.: Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1940, supp.; footnote 1 *a*. Paige, Cowen and Wolf.[1c]

TABLE 2.—*Analysis of Symptoms and Signs in Fifteen Cases of Infantile or Congenital Toxoplasmic Encephalomyelitis* *

	Cases Diagnosed at Autopsy														
	Authors' Series I					Cases Identified from Literature (Not Originally Recorded as Toxoplasmic Encephalomyelitis)				Cases Diagnosed Clinically Authors' Series II					
	J. S.[1a] Case 1	C. D.[1b] Case 2	L. M.[1c] Case 3	B. R.[1c] Case 4	A. M. T.[1c] Case 5	Janku[12a] Wolf and Cowen[1a]	Margarinos Torres[12b] Wolf and Cowen[1a]	Richter[12c] Wolf and Cowen[1a]	de Lange[12d] Paige, Cowen and Wolf[1c]	P. D. Case 1	J. F. Case 2	A. I. Case 3	M. B. Case 4	D. H. Case 5	C. J. Case 6
Anamnestic data															
Sex	♀	♂	♀	♂	♀	♂	♀	♀	♀	♀	♂	♂	♀	♂	♂
Race	W	W	W	N	W	W	W	W	W	W	W	W	W	N	W
Age at onset	2 days	3 days	At birth	.....	2 days	3 days (?)	At birth	6 wk. (?)	9 days (?)	1st wk. (?)	At birth	4th day	2 mo.	4 yr. (?)	3 mo.
Duration of illness	28 days	28 days	9 wk.	.....	1½ days	11 or 16 mo.(?)	2 days	1 wk.(?)	4 mo.	5 yr.	14 mo.	3 yr.(?)	4½ yr.	7½ yr. (?)	8 yr.
Age at death	30 days	31 days	9 wk.	Stillbirth	3½ days	11 or 16 mo.(?)	2 days	7 wk.	4 mo.	Living	Living	Living	Living	Living	Living
Symptoms and signs															
Neurologic															
Convulsions	+	+	+	..	−	+	+	+	−	+	−	−	−	−	+
Petit mal	−	−	−	..	−	−	−	−	−	−	−	−	−	+	−
Muscle twitching or tremors	+	−	+	..	−	−	..	+	+	−	−	−	−	−	−
Head retraction	+	+	−	..	−	−	..	−	−	−	−	−	−	−	−
Opisthotonos	+	−	−	..	−	−	..	+	−	−	−	−	−	−	−
Evidence of transverse myelitis	−	+	−	..	−	−	..	−	−	−	−	−	−	−	−
Internal hydrocephalus	+	±†	+	+	−	+	..	+†	+	+	+	−	−	−	−
Microcephalus	−	±‡	−	..	−	−	..	−	−	−	−	+	−	−	−
Speech difficulty	..	..	..	..	..	..	..	..	..	+	..	+	+	−	±
Mental deficiency or psychomotor retardation	..	..	..	..	..	..	..	..	..	+	+	+	−	+	−
Ocular															
Focal chorioretinitis	+	+	+	+	..	+	..	..	−	+	+	+	+	+	+
Microphthalmos	−	−	+	+	−	+	..	..	−	−	+	−	+	−	+
Strabismus or other ocular signs	−	−	+	..	−	+	..	..	−	+	+	+	+	+	+
Other symptoms and signs															
Jaundice	−	−	−	..	−	−	..	−	−	−	+	+	−	−	−
Splenomegaly	−	−	−	..	+	−	..	−	−	−	+	+	−	−	−

Hepatomegaly	—	—	—	..	+	—	..	—	—	—	+	+	—	—	—
Maculopapular rash	—	—	—	..	—	—	..	—	—	—	±	+	—	—	—
Feeding difficulty	—	—	—	..	—	—	..	..	+	+	—	—	—	—	—
Diarrhea or vomiting	+	+	—	..	—	+	..	..	+	±	—	—	—	—	—
Pulmonary signs	—	—	—	..	+	±	..	..	—	+	±	—	—	+	—
Lymphadenopathy	—	—	—	..	—	—	..	—	—	—	±	—	—	—	—
Fever	+	±	—	..	+	—	..	+	+	—	±	—	—	—	—
Subnormal or labile body temperature	+	+	+	..	—	+	..	..	+	—	—	—	—	—	—
Calcification in brain (roentgenogram or autopsy)	+‡	+	+	+	—	..	..	+	+	+	+	+	+	+	—
Laboratory data															
Cerebrospinal fluid															
High protein	+	+	+	..	..	..	..	+	+†	—	+	..	..	..	..
Xanthochromia	+	+	+	..	..	..	..	+	..	+	+	..	..	..	..
Pleocytosis	+	..	..	..	..	..	..	±	..	+	+	..	..	..	..
Blood															
Anemia	—	—	+	..	—	..	..	+	..	—	+	+	—	—	..
Leukopenia	±	±	±	..	—	..	..	—	..	—	—	—	—	—	..
Leukocytosis	—	—	+	..	+	..	..	+	..	—	—	—	—	—	..
Wassermann, Kline or Kahn test	—	—	—	—§	—§	..	..	..	..	—	—	—	—	—	..
Neutralization test for toxoplasmosis	..	..	..	..	..	..	..	..	..	+	+	+	+	+	+
Neutralization test—serum of mother	..	..	+	+	+	..	..	..	..	—	+	—	—	+	..
Toxoplasma in smears of cerebrospinal fluid	+	..	..	..	..	..	..	..	..	+	—	..	..	..	..
Toxoplasma isolated by animal inoculation of cerebrospinal fluid	..	..	..	..	..	..	..	..	..	—	+	..	..	..	..
Toxoplasma isolated by animal inoculation of patient's brain tissue	..	+	+	..	..	..	..	..	..	..	..	..	..	..	..
Autopsy: characteristic lesions containing toxoplasmas	+	+	+	+	+	+	+	+	+	..	..	..	..	..	..

* In this table a leader (..) indicates that no examination was made or that information was not available or was inapplicable; —, that the reaction was negative or the sign was not present; +, that the reaction was positive or the sign was present; ±, that the result was slightly positive or doubtful.

† The condition was found at autopsy and was not noted clinically.

‡ The condition was not originally recorded but was noted on reexamination.

§ The test was made on the mother's blood.

were born at full term; 4 were somewhat premature, and in 1 instance the duration of gestation was not known.

Condition at Birth.—The condition of 5 patients was good at birth, 3 were somewhat asphyxiated, 1 was stillborn, and concerning 6 information was not available.

Onset.—The earliest symptoms and signs were noted at birth or in the neonatal period in most of the patients. In the remainder the onset seemed to be later, but in most instances the inception was clearly during infancy. In only 1 patient were the first recorded symptoms of later date. When the history began beyond the neonatal period, however, there were often indications that the disease had probably been present since birth. The first obvious sign in 1 infant was left internal strabismus, noted at 2 months of age, while left microphthalmos, observed much later, suggested a congenital origin of the infection. Another infant showed evidence of impaired vision, nystagmus and strabismus at 3 months of age. Abnormal movements of the eyes, however, were said to have been present at birth, and ophthalmoscopic examination at 6 years revealed chorioretinal lesions, which were considered congenital. A third child, exhibiting left external strabismus and complaining of pain in the eyes at 4 years of age, was examined by a competent ophthalmologist, who expressed the belief that the ocular lesions were of prenatal origin. In 8 patients the earliest signs were seen during the first four days of life. In 2 patients they appear to have begun approximately at 2 weeks of age and in 1 at 1½ months of age. It is not improbable, however, that earlier signs were overlooked in the last 3 infants or that the disease was already present, without obvious signs.

The first recorded symptoms and signs were variable. Convulsions were the earliest manifestation in 3 patients. Enlargement of the head due to hydrocephalus was noted at birth in 2 of the children. Two infants had neonatal jaundice, which persisted late into the second month of life. Two infants presented feeding problems in the first weeks of life. In 1 of these patients fever appeared on the twelfth day and enlargement of the head on the sixteenth day; in the other patient, ocular disturbances and convulsions occurred at the age of 5 months. One infant had signs of respiratory disturbance at 2 days of age, and another, a "cold" followed by fever and convulsions at 6 weeks of age.

Symptoms and Signs.—Neurologic Symptoms and Signs: Convulsive seizures: Convulsions were commonly observed and occurred in 9 of the 15 patients. Three of the patients had generalized seizures during the first few days of life, with infrequent and irregular recurrences during an illness of less than a month. One of these patients had an initial right-sided jacksonian attack. Two infants, who died at about

2 months of age, had generalized convulsions in the terminal portion of their illness. Similar seizures late in the course of a protracted illness occurred in an infant who died early in his second year. Three children, who have survived beyond infancy, and are now 5, 8 and 11½ years of age respectively, continue to have recurrent seizures. In the first 2 children these seizures began in infancy, are generalized and have become less frequent in recent years. The third, and oldest, child began to have frequent petit mal attacks with loss of consciousness beginning at 7 years of age and continuing through four years.

Internal hydrocephalus: Clinical or roentgenographic evidence of internal hydrocephalus was noted in 7 patients, while in 2 it was not discovered until autopsy. Six infants showed enlargement of the head, observed during the first month of life in all but 1, in whom it was first recorded at 3 months of age but may have been present earlier. In 1 patient of this group the condition was diagnosed before birth and necessitated craniotomy to permit delivery, and in another there was evidence of hydrocephalus at birth. In 1 of the children, who is still alive, roentgenograms of the skull and ventriculograms at 3½ years of age revealed the presence of considerable internal hydrocephalus. In most of the children the hydrocephalus was of considerable degree.

Microcephalus: In 1 patient microcephalus was noted at 5 months of age, and a second presented roentgenographic evidence of slight microcephaly. In this case the ventricles were slightly dilated, but the destruction of cerebral tissue, observed at autopsy, would account for the mild microcephalus. The first child is still alive. The evidence of widespread intracerebral calcification indicates that considerable cerebral damage has occurred, and this loss of cerebral tissue probably accounts for the microcephalus.

Other neurologic symptoms and signs: As might be expected from the wide distribution of the lesions in the central nervous system, there were no constant findings. As has been indicated, convulsive seizures were common and twitching and tremors of the extremities frequent. Retraction of the head or opisthotonos occasionally occurred. Two patients had spastic contractions of the extremities. Difficulty in sucking and swallowing was noted in 1 infant. Another had signs of a transverse high cervical lesion of the spinal cord, which included a Horner syndrome and evidence of a subarachnoid block.

In the series of patients who survived beyond infancy for from one to ten years and are still alive, no frank motor, sensory or cranial nerve deficiencies were noted, other than those listed under "ocular signs." Two patients had continuing generalized convulsions and another petit mal attacks. Retardation of mental and speech development occurred in a number of the patients. Two children showed hyperactivity and presented behavior problems.

Ocular Signs: Six patients had microphthalmos, which was bilateral in 2 and unilateral in the others. Two showed remnants of pupillary membrane in one eye and narrowed palpebral fissures. One had, in addition, a posterior cortical cataract, and the other, a posterior lenticonus and naevus flammeus of the left upper lid and brow. Two patients having microphthalmos also showed enophthalmos, and this was present in 1 patient having eyes of normal size. Nystagmus and nystagmoid movements of the eyes, deviation of the head and eyes to one side, impairment of ocular movements and abnormal pupillary reactions were sometimes noted. Strabismus was frequently present.

The most striking and frequent ocular signs were those observed in the eyegrounds. Of the 11 patients examined ophthalmoscopically, 10 showed chorioretinal lesions, and the 1 patient who did not had only a single examination, in which no special search for such lesions was made. In the stillborn infant necropsy revealed typical lesions. The remaining 3 children had no clinical or postmortem examinations of the fundus.

The focal chorioretinal lesions were severe and extensive and were nearly always bilateral. The macular region was regularly involved, but the peripheral portions of the eyegrounds were also frequently affected. The lesions so far observed were almost entirely quiescent or healed. In only 1 instance was comparatively early and active chorioretinitis seen, which progressed to an inactive stage. The old lesions were sharply marginated areas of chorioretinal atrophy and proliferation of varying degree with diffuse irregular pigmentation, which often formed a marginal band at the periphery. These patches of chorioretinitis were oval, circular, ovoid or irregular, and the majority varied in size from 1 to 6 disk diameters. They were sharply marginated, slightly elevated or concave, yellowish white, white and reddish brown lesions, stippled and often bordered with brownish black and black pigment. Except in a few instances, the lesions in each eye were multiple, ranging from two to twelve. The retina and its vasculature intervening between the lesions appeared normal. The media were nearly always unclouded. At times masses of proliferating tissue grew forward into the vitreous. In 1 instance such tissue bridged from one lesion to another, and in another it filled a good part of the vitreous.

In the 1 instance in which relatively early and active lesions were seen, the most acute lesion was in the macular area. It was homogeneous, somewhat raised, reddish brown with a bluish cast, poorly marginated and edematous. There was a central, shallow umbilication at its flattened apex, which was light orange-brown and approximately in the position of the fovea. A somewhat more advanced lesion in the macular area of the other eye of the same patient was also an indefinitely marginated zone of edema of the same color, having a diffuse marginal band of grayish brown pigment and a central whitish area of chorioretinal atrophy, bordered by brown and deeply situated black pigment.

The optic disks were noted to be atrophic in a number of patients. The atrophy was of the primary type due to destruction of the macula and of other portions of the retina. Atrophy secondary to papilledema was present in 1 patient.

Additional Symptoms and Signs: Splenomegaly and hepatomegaly: Three of the patients had moderate or marked enlargement of the spleen and liver, which was noted during the first two weeks of life. One of these infants died at 3½ days of age. The other 2 are still alive, and in 1, who was reexamined at the age of 7½ months, the spleen was no longer palpable but the liver was still somewhat enlarged. In the other patient, reexamined at 2 years of age, the spleen and liver were no longer palpable. The infant who died showed no lesions or organisms in the liver or spleen at necropsy. In animal toxoplasmosis the liver and spleen are commonly involved.

Jaundice: The 2 infants with splenohepatomegaly who survived had icterus, beginning at birth in 1 instance and at 4 days of age in the other. It lasted about two months in each case.

Cutaneous eruption: A diffuse maculopapular rash occurred in the 2 infants with jaundice, beginning on the sixth day in 1 and on the ninth day in the other. It was transient in 1 child and lasted about three weeks in the other, and was followed by desquamation.

Symptoms of respiratory disturbance: These symptoms varied in type and severity and may have been incidental to bacterial infection. The frequency of pulmonary lesions in animal toxoplasmosis, their occurrence in adult human toxoplasmosis and the demonstration of toxoplasmic interstitial pneumonitis in 1 of our infants, aged 3½ days, on whom autopsy was performed, indicate that symptoms and signs of involvement of the respiratory tract may have been the result of toxoplasmic infection of the lungs. The child showing toxoplasmic pneumonitis at necropsy had definite pulmonary signs on the second day of life. One infant had transient bronchitis and another a "cold" at approximately 2 months of age. A patient, now 5 years of age, had attacks of pneumonia at 1, 2 and 3 years of age. A Negro boy of 11, the oldest surviving patient, had asthmatic attacks at the age of 3, which were thought to be allergic, and is at present suspected of having pulmonary tuberculosis.

Terminal symptoms of respiratory involvement, such as Cheyne-Stokes respiration, were presumably due to intracranial toxoplasmic lesions.

Gastrointestinal symptoms: Five of the patients were subject to vomiting, diarrhea or both, these disturbances being of minor severity. One of these children and another infant presented feeding problems.

Circulatory disturbances: An infant with edema of the lower extremities and genitalia was observed at autopsy to have diffuse toxoplasmic myocarditis.

Temperature: Of those patients who did not survive infancy, it may be said in general that there was a tendency toward normal temperature early in the disease and an unstable temperature with frequent elevations and drops to a subnormal level in the later stages. This lability in temperature was probably due to a disturbance in heat regulation arising from lesions in the floor of the third ventricle. The children who survived beyond the first year of life had no definite history of prolonged periods of pyrexia which might be attributed to chronic toxoplasmosis, nor did they have any fever or other abnormalities of temperature during the periods of observation.

Roentgenographic Observations: Calcification in brain: The necrotizing cerebral lesions of toxoplasmic encephalomyelitis have been shown to calcify readily. Such calcium deposits have been observed in a stillborn child with fully developed toxoplasmosis, as well as in infants dying at the end of the first month of life. The roentgenographic demonstration of such calcification is one of the outstanding clinical features of toxoplasmic encephalomyelitis. In 9 of the 15 cases under discussion roentgenograms were made of the skull, and of these intracranial calcification was shown in 8. In 6 there was bilateral cerebral calcification, appearing as small, rounded shadows. These lesions varied considerably in number and averaged approximately 1 to 3 mm. in diameter. They occurred in the cortex of all the cerebral lobes and in the basal ganglia and thalami. In the last two structures the calcium deposits occasionally appeared as curvilinear streaks. Of 2 instances in which unilateral calcification was observed, a small deposit was noted in the caudate nucleus in 1 and faint shadows in the postcentral region in the other. In 3 additional cases in which roentgenographic examination was not made intracerebral calcification was observed at necropsy.

Other roentgenographic changes: Enlargement of the skull and fontanels, separation of the sutures and pneumencephalographic evidence of dilatation of the ventricles gave indication of internal hydrocephalus in a number of cases. In 1 of the older children there was, in addition, atrophy of the posterior clinoid processes and dorsum sellae. The dilatation of the lateral ventricles was in some instances much less marked in the frontal horns than elsewhere. This asymmetric enlargement of the ventricles was probably due, not to obstruction alone, but to the added factor of unequal necrosis of the ventricular walls. In 2 cases the protein of the ventricular fluid was high and gas bubbles persisted, producing a honeycombed pattern in the ventricles.

Cerebrospinal Fluid: Examinations of the cerebrospinal fluid were made in 6 cases. The fluid obtained by lumbar or cisternal puncture was under normal pressure when this was determined, was xanthochromic, had a high protein content and in 4 instances showed pleocytosis. Differential counts were unsatisfactory, but lymphocytes seemed to predom-

inate. Red cells, presumably not introduced by trauma associated with the diagnostic procedure, were present in several instances. In 2 cases the dextrose and chloride were somewhat lower than normal.

The ventricular fluid was examined in 4 cases, repeated tests being made in 3. The cerebrospinal fluid pressure was somewhat raised on the first examination in all but 1 instance. Later examinations revealed a normal pressure. The fluid was xanthochromic or turbid. In 2 instances there was pleocytosis, with predominance of lymphocytes, and in 1 of these occasional eosinophils were seen in one smear. A high protein content was a constant feature. The dextrose and chloride contents were low in 3 cases. In 1 case there was evidence that as the disease progressed the pleocytosis and the protein content of the cerebrospinal fluid diminished.

Blood: Examination of the blood was carried out on 10 patients. Three showed relative leukopenia, the leukocyte count ranging from 5,200 to 8,000 per cubic millimeter. The average normal white cell count during the first month of life, when these observations were made, is approximately 12,000 cells per cubic millimeter. The great variation in the normal leukocyte count at this age, however, must make one cautious in evaluating the significance of this result. One of the children with leukopenia and 3 others had a moderate degree of anemia. These observations were made in the first months of life, during the early stages of the disease. One of the children showing leukopenia and 2 others who died during this early period exhibited terminal leukocytosis. In 1 child this was associated with supervening bacterial infection. The patients who survived showed a return of their red and white counts to normal or, having been first observed at a later stage of the disease, presented a normal blood picture at that time. The differential count showed no consistent changes. A questionable eosinophilia was noted in 1 case.

Course.—Our early experience with infantile or congenital toxoplasmosis led us to believe that it was an acute or subacute infection which in most cases ended fatally within the first few months of life. Since then it has become evident that survival beyond infancy does occur and may prove to be the rule. The present condition of a few of the survivors suggests that they may well go on to reach adult life. The observed tendency toward healing of toxoplasmic lesions may possibly result in a quiescent state of the infection or in complete disappearance of the protozoon. The persisting symptoms and signs would then depend on the extent of the original neural and ocular injury and on the result of possible interference with the cerebrospinal fluid circulation.

The most severe incapacitation to which the surviving children are subject is diminution in vision, and this may be their presenting symptom. As has already been pointed out, retardation in the acquisition of

speech and mental deficiency may occur. The latter is usually mild in degree. Generalized convulsions or petit mal attacks may be a prominent persisting symptom. Chronic hydrocephalus may be present.

CORRELATION OF CLINICAL AND PATHOLOGIC OBSERVATIONS

In previous reports of this series we have described in detail the pathologic changes in cases in which autopsy was performed. Although

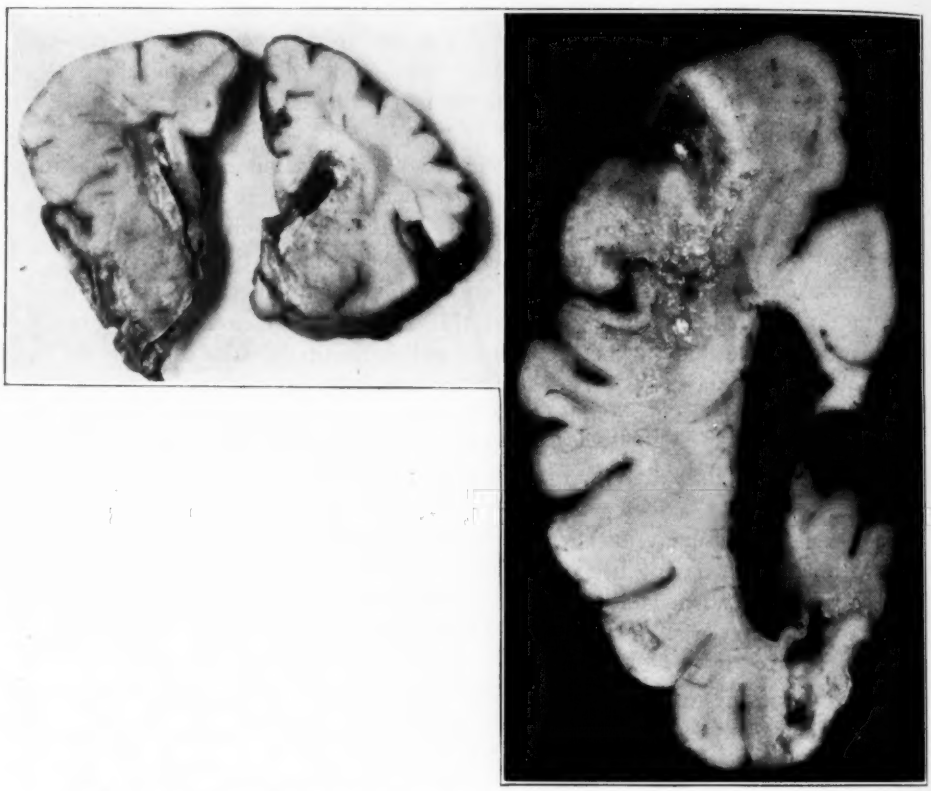

Fig. 7.—Periventricular and cortical necrosis in a case of toxoplasmic encephalomyelitis.

none of the patients had survived beyond infancy, some of the lesions were obviously healed, and those in the surviving patients, whose cases are now under discussion, may be similar.

Central Nervous System.—The lesions in infantile toxoplasmosis are most severe in the cerebrum, and here they are most intense in the cortex, the basal ganglia and at times the periventricular areas (fig. 7). They are marked by inflammation and necrosis and by the formation of char-

acteristic miliary granulomas (fig. 8). The necrosis is often followed by calcification (fig. 9) and associated gliosis, and at times by fibrosis. This tendency of healing lesions to calcify explains the common finding of shadows of calcium density in roentgenograms of the skull. When the cortical degeneration is severe, it obviously may be the basis for the mental retardation observed in some of the older children. It is likely that such involvement of the cortical areas governing speech leads to the deficiency in that function. The occurrence of convulsions and petit mal

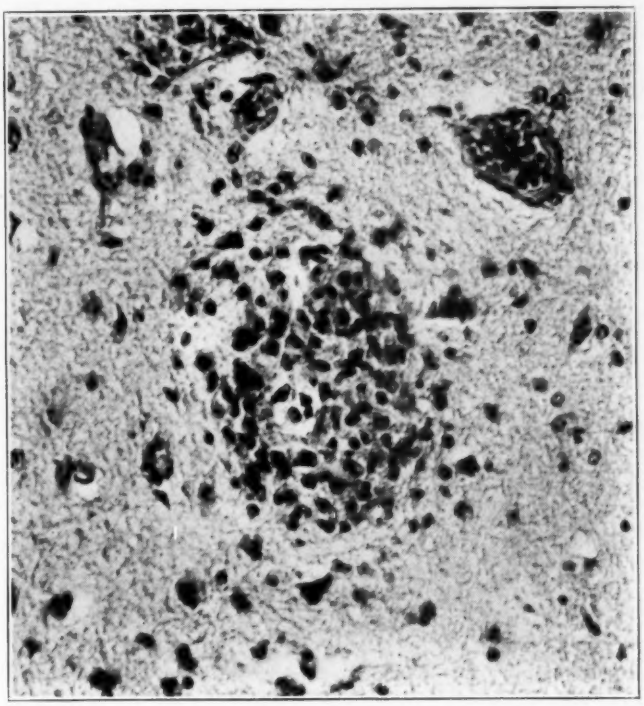

Fig. 8.—Miliary granuloma in brain stem in a case of toxoplasmic encephalomyelitis.

attacks is also attributable to the cortical damage. Other focal signs are due to localized lesions. Transverse myelitis and a Horner syndrome in 1 infant were found to be the result of an inflammatory and necrotizing lesion in the cervical portion of the cord, and difficulty in sucking and swallowing is probably secondary to the frequent lesions of the brain stem.

Internal hydrocephalus is often present and appears to be secondary to two factors. One is the stenosis or occlusion of the aqueduct of Sylvius or the interventricular foramens due to ependymitis. The other

is the intense periventricular necrosis, which produces secondary enlargement of the ventricular cavities because of actual loss of tissue. The high protein content of the ventricular fluid may be the result of the continuing inflammation within ventricles which are partially obstructed. Occasional microcephalus would seem to be the result of severe necrosis and loss of cerebral tissue.

Eyes.—Reduction of vision is evidently the consequence of the widespread destruction of the retina, in particular, the involvement of the macular region by the specific lesions. The latter give rise to the striking ophthalmoscopic picture. The frequent strabismus and nystagmus

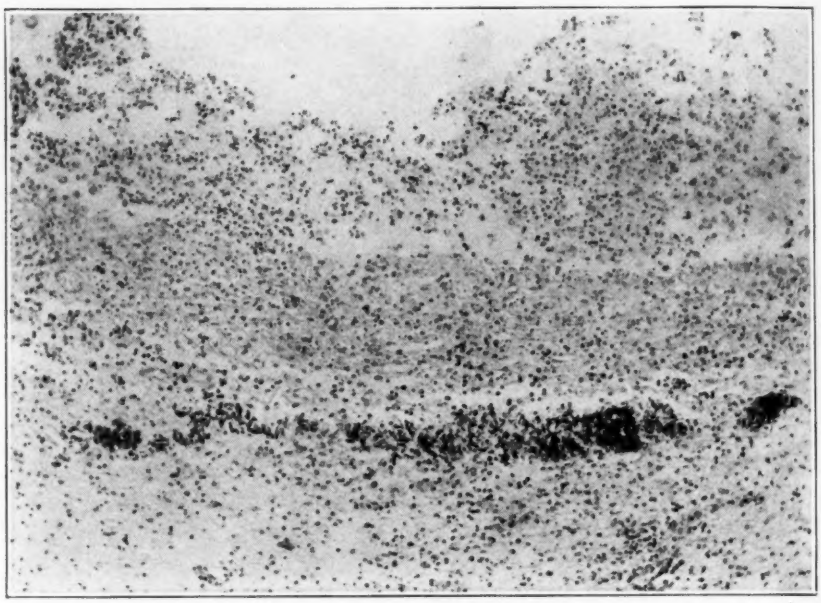

Fig. 9.—Necrosis of wall of lateral ventricle in a case of toxoplasmic encephalomyelitis. Note inflammation and calcification.

may be the result of the partial blindness or of the common lesions of the brain stem. Microphthalmos and associated minor abnormalities of the eye probably result from interference with its development following infection late in intrauterine life.

Other Organs.—Specific interstitial pneumonitis was present in 1 infant on whom autopsy was performed. Although pneumonic signs in this patient and in some others who survived were vague and fleeting, it is possible that they may have been due to toxoplasmic lesions of the lungs. The anemia is unexplained as yet. The occurrence of toxoplasmas in the bone marrow in various animals and the infection of red

blood cells in birds [14] raises the question whether such lesions may be the cause of anemia. Similar observations, however, have not as yet been made on man. The cause of the splenomegaly and hepatomegaly is not known. Although no toxoplasmic lesions were seen in the liver or spleen in the infant with splenohepatomegaly on whom necropsy was performed, the frequent occurrence of focal lesions in these organs in animals suggests that such pathologic changes may be the cause of the enlargement in other instances. No cutaneous lesions have as yet been examined in the cases of infantile toxoplasmosis, so that the nature of the maculopapular eruption is not known. They may be nonspecific. On the other hand, by comparison with the cutaneous lesions in cases of adult toxoplasmosis, it is possible that they may represent focal inflammatory lesions in the corium and subcutaneous tissue. The finding of parasites in the skin by Magarinos Torres,[12b] who, however, mentioned no actual lesions, strengthens the possibility that the lesions may be specific.

OTHER FORMS OF HUMAN TOXOPLASMOSIS

The recognition of the occurrence of human toxoplasmosis in the form of encephalomyelitis in infants was followed by its identification as a disseminated infection in adults and as acute encephalitis in older children.

Pinkerton and Weinman described a 22 year old Peruvian [4a] who showed clinical evidence of infection with Bartonella bacilliformis and died after an illness of twelve days. Autopsy revealed widespread toxoplasmosis, involving the heart, lungs, spleen, adrenals, kidneys, liver, brain, lymph nodes and subcutaneous tissue. Pinkerton and Henderson [4b] subsequently described 2 fatal cases of acute febrile, exanthematous disease in adults due to Toxoplasma. The symptomatology resembled that of the typhus–spotted fever group. Malaise and weakness were followed by abrupt onset of chills and fever and by the appearance of a maculopapular eruption involving almost the entire body except the palms, soles and scalp. Pulmonary involvement in both instances appeared to be the cause of death. There were no neurologic symptoms or signs. Autopsy revealed interstitial pneumonitis and focal lesions in the liver, spleen and subcutaneous tissues. In 1 case small numbers of lesions were seen in the brain.

Coincident with the description of adult toxoplasmosis, acute encephalitis was reported by Sabin in 2 older children, boys 6 and 8 years old.[3] Each child had mild, fluctuating fever, which in 1 instance did not begin until the second week of the illness. The boy of 6, for whom the disease was fatal, became delirious, had clonic and tonic movements of the extremities, continued to have generalized convulsions, manifested terminal continuous muscular twitchings and died on the thirtieth day of his illness. The other child continued to have convulsions, became

14. (*a*) Wolfson, F.: Mammalian Toxoplasma in Erythrocytes of Canaries, Ducks and Duck Embryos, Am. J. Trop. Med. **21**:653-658, 1941. (*b*) Manwell, R. D.: Avian Toxoplasmosis with Invasion of the Erythrocytes, J. Parasitol. **27**:245-251, 1941.

irrational and then suddenly, after ten days, became quite well again. In each instance it was noteworthy that there were no signs of meningeal irritation or involvement of cranial nerves.

Examination of the cerebrospinal fluid of each child showed pleocytosis, the cell count of the fluid in 1 case rising to 200 cells per cubic millimeter, chiefly mononuclear elements, and in the other, to 300 cells, chiefly lymphocytes. The blood count was normal in the fatal case and the child who recovered presented leukocytosis, with a white cell count of 20,000, 90 per cent of which were polymorphonuclears. One patient had generalized lymphadenopathy and an enlarged spleen, and the other had moderate cervical and inguinal lymphadenopathy.

Although the infantile, or congenital, form of the infection seems to be a clearcut clinical and pathologic entity, with the 15 cases now on record, it is too early to draw permanent distinctions between it and the juvenile and adult forms of toxoplasmosis until additional instances of the latter are reported. It is of interest, however, to note the differences in the three types which are apparent to date. In the infantile form of the infection, the central nervous system is constantly and predominantly affected and the eyes are usually involved. Here the pathologic lesions are severe and extensive and contain large numbers of readily identifiable toxoplasmas. The involvement of other tissues is inconstant, often slight. Toxoplasmosis, beginning in the juvenile period, appears to differ from that beginning in infancy in which the children survive into the juvenile period. This juvenile form of toxoplasmosis is as yet represented only by 2 cases, in 1 of which autopsy was performed. If the postmortem observations are representative, this type differs from the infantile, or congenital, form in that the lesions in the nervous system are much milder. They are not visible grossly and do not show massive necrosis and inflammation or calcification histologically. Toxoplasmas were present in the lesions, but were relatively few. The difference, however, would seem to be one of degree, since there is a similaritiy between the milder lesions of the infantile form and those of the juvenile type. Clinically, the onset in the 2 known cases was at 6 and 8 years of age respectively, and the symptoms were those of acute encephalitis with a febrile course, in which ocular lesions and other prominent features of the infantile form of the disease were absent. Lymphadenopathy and enlargement of the spleen were described in cases of the juvenile form. In cases of adult toxoplasmosis, as in those of the juvenile type, only mild, infrequent lesions of the central nervous system have been noted. There are, on the other hand, disseminated, focal, necrotizing lesions in other organs and interstitial pneumonia. Lesions in the viscera, although infrequent, occur in the infantile form, and in a case in which the lesions in the brain were least developed, the changes in the other organs were intense and resembled those in cases of the adult form. Chorioretinitis and intracranial calcification were not present in the latter. Clinically,

the adults had a short, febrile illness, marked by chills, a generalized maculopapular eruption and signs of pneumonia. In 2 of the infants a cutaneous eruption occurred early in the illness.

Since some of the patients who seem to have been born with toxoplasmosis survive into the juvenile period, and will perhaps be found to reach adult life, the classification of cases under the infantile, juvenile and adult forms of the disease may lead to confusion. It might be preferable to refer to the disease as congenital toxoplasmosis when the evidence points to intrauterine inception of the infection, and as acquired when the disease has obviously begun in the juvenile or the adult period. In some of the cases of the infantile form the disease may also prove to be acquired.

EPIDEMIOLOGY

Infantile, or congenital, toxoplasmic encephalomyelitis was at first thought to be rare, but further experience has indicated that this is only apparent and that many cases of the disease are probably unrecognized. The fact that 11 cases have been encountered in a single clinic within a period of five years certainly suggests that the disease is not uncommon. Knowledge as to the distribution of the human infection is obviously scanty. Our 11 patients were born in and about New York city. In view of the probability that the disease is acquired during prenatal life, the birthplace and the places of residence of the parents may be of interest. Two of the mothers were born in the British West Indies, while the remainder were American born. The majority were born in and about New York city and had resided there most of their lives. All had lived in New York city for some time prior to their pregnancy. Travel had in most cases been limited and local. With few exceptions, it had been confined to the northeastern seaboard of the United States. The fathers had lived most of their lives in New York city. The majority were born in the United States, and of the remainder, 2 were British West Indians, 1 was Italian, 1 Scotch and 1 Danish.

Among the 4 authenticated cases from the literature, 1 infant was born in Prague, Czechoslovakia,[12a] another in Rio de Janeiro, Brazil,[12b] a third in Chicago[12c] and a fourth in Amsterdam, Netherlands.[12d] Through personal communications from colleagues in other cities,[15] cases are known to have recently been recognized in Detroit; Boston; Nashville, Tenn., and Dallas, Texas. The juvenile form of toxoplasmosis was reported from Cincinnati and the adult type from St. Louis.

Although a relatively small number of cases are as yet available for consideration, it is clear that infantile, or congenital, toxoplasmosis is widespread, since it has been recognized on three continents. This cor-

15. Dr. G. Steiner, of Detroit; Dr. B. Crothers, of Boston; Dr. W. de Gutiérrez-Mahoney, of Nashville, Tenn., and Dr. P. M. Levin, of Dallas, Texas.

responds to the wide geographic distribution of animal toxoplasmosis.[1b] The latter has been reported chiefly in rodents and birds from most parts of the world. This reservoir of animal toxoplasmosis is probably the source of human infection. The mothers of the children having infantile toxoplasmosis were questioned as to animal contacts, and it was found, as might be expected, that they had been exposed to common barnyard and household mammals and birds. No definite leads were discovered. In some of the homes mouse infestation was severe, and the fact that infection of rodents with Toxoplasma is common suggested an etiologic connection. Some of the households of the other patients were free of vermin, however, so that too much weight could not be placed on this factor. Similar limited data concerning contacts with rabbits, birds and dogs also yielded no suggestive source of infection.

The problem of transmission of the infection from animal to animal and from animal to man is as yet unsolved. Whether this occurs by direct contact or through the mediation of a vector is unknown. The contamination of food by mouse excreta, for instance, was considered in the 2 instances in which the home was infested with mice, since mice had been seen in the food bins.

Chatton and Blanc [16] collected various ectoparasites of the gondi (Ctenodactylus gondi), a North African rodent spontaneously infected with Toxoplasma, and considered their possible role as vectors of toxoplasmosis in this animal. The parasites included two species of ticks, a mite, a flea and two species of mosquitoes. One of the ticks (Rhipicephalus sanguineus) was particularly prevalent, and the authors pointed out that many other animals, including the dog and the rabbit, which are known to be hosts of Toxoplasma, are also hosts of this tick. The ubiquity of the tick recalled that of Toxoplasma and led Chatton and Blanc to suppose that this arachnid might be the intermediate host of Toxoplasma in the gondi, and perhaps the host of Toxoplasma in other mammals. However, the presence of Toxoplasma in the tick could not be verified by direct examination or by inoculation of gondis with ground-up ticks. The authors cite a similar negative inoculation experiment by Nicolle. The role of a mite, Trombidium (species[?]), as a vector of Toxoplasma in the gondi was also discussed but could not be substantiated. In the recent description of adult toxoplasmosis, a history of tick bites was obtained in 2 cases.[4b] The significance of this is conjectural until further investigations are carried out.

Since it is probable that infantile toxoplasmic encephalomyelitis begins in utero, the date of birth may be used as a rough index of the seasonal incidence of the disease. Of the 15 patients with this form of

16. Chatton, E., and Blanc, G.: Notes et réflexions sur le toxoplasme et la toxoplasmose du Gondi, Arch. Inst. Pasteur de Tunis **10**:1-40, 1917.

toxoplasmosis, the birth dates of 12 were known. Eight of these children were born in the five month period between mid-April and mid-August. The other 4 were born in the three month period between early December and late February. The possible significance of this seasonal distribution cannot be evaluated until further statistics have been gathered.

PRENATAL INCEPTION OF THE DISEASE

In previous publications of this series, evidence was presented for the intrauterine origin of the infection.[17] This, in brief, depended on the demonstration that in some of the cases the lesions must necessarily have been present before birth. The most striking of these cases was that of the fetus, in which a diagnosis of hydrocephalus was made ante partum, necessitating craniotomy for delivery. This stillborn infant had a full blown toxoplasmic encephalomyelitis. The onset of symptoms and signs soon after birth in the other cases seemed to support this view. The chronic appearance of the pathologic lesions, which were often extensively calcified, made it unlikely that they could have developed during the short extrauterine period.

In the present group of clinical cases, the patients for the most part came under our observation at a later period. In the section describing the onset of the disease, however, it may be noted that a history of symptoms or signs beginning at or shortly after birth was obtained in most instances. It would seem, then, that these additional clinical cases tend to support the thesis that infantile toxoplasmosis begins as a fetal infection.

One difficulty in this interpretation is that the mothers have been consistently healthy. It may be that they harbor a latent infection, similar to the symptomless toxoplasmosis of many animals. Their past histories do not reveal any illness which might have been the manifest disease.

The blood of the mothers of 3 of the infants on whom necropsy was performed was examined for antitoxoplasmic activity in the manner described previously. In all 3 instances (cases 3, 4 and 5, series 1) the neutralization test gave positive results. Five of the mothers of the 6 infants with a clinical diagnosis of toxoplasmosis were similarly tested. The results for 3 were negative. These were the mothers in cases 1, 3 and 4, series 2. The reactions for 2 of the mothers (cases 2 and 5, series 2) proved to be positive. Thus, 5 of 8 mothers examined gave positive, or suggestively positive, evidence of the presence of neutralizing antibodies to Toxoplasma in their blood. These results may be variously interpreted. First, there may be a widespread, inapparent infection of

17. Wolf, A.; Cowen, D., and Paige, B. H.: Fetal Encephalomyelitis: Prenatal Inception of Infantile Toxoplasmosis, Science **93**:548-549, 1941. Paige, Cowen and Wolf.[1c]

the general population, sufficient to produce immunity, and the mothers may have been in this group. In this case, the acquisition of the infection by the infant would be unrelated to that of the mother. This seems unlikely. Another possibility is that the infants acquired the infection immediately post partum and that the mothers were secondarily infected. The third possibility, which to us seems a probability, is that the mothers had a clinically inapparent infection which was transmitted to their offspring in utero.

If the infection, as we believe, is acquired during prenatal life, the question of the site of infection in the mother arises. No direct knowledge on this point is as yet available. The possibility that infection of the placenta leads to infection of the fetus has been considered. Unfortunately, only one poorly preserved placenta was available for examination, which yielded negative results. The possibility that the amniotic fluid may be affected by an ascending infection from the vagina suggests itself. The presence of Toxoplasma in the vaginas of the mothers has not been demonstrated, however.

One observation may have some bearing on the question of an ascending infection. In 4 of our 11 cases the membranes ruptured prematurely. In 1 instance this occurred two weeks before delivery, in another, a week prior to birth, and in the other two, several days before the onset of labor. A possible portal of entry for vaginal organisms might thus be established. However, in the majority of cases the membranes were intact until labor began. The question of the site of the infection in the mother is thus unanswered.

DIAGNOSIS

The 6 cases presented in this report are the first clinically diagnosed instances of infantile toxoplasmic encephalomyelitis. A brief review of the chief diagnostic features may be of value.

The clinical picture of infantile, or congenital, toxoplasmic encephalomyelitis may be divided roughly into an acute or subacute phase, in which the infection is probably active, and a later phase, in which the clinical manifestations are chiefly residual effects of the infection.

A review of the symptomatology of the early phase as previously described, reveals the following chief features: (1) onset at birth or shortly thereafter; (2) convulsions; (3) hydrocephalus, clinically apparent or demonstrable by pneumencephalography; (4) other, inconstant neurologic symptoms, such as tremors, twitches, spastic contraction of the extremities and evidence of transverse myelitis; (5) bilateral, focal chorioretinitis, almost invariably involving the macula; (6) other ocular signs; such as microphthalmos and ocular palsies; (7) intracerebral calcification, often multiple and bilateral, and involving the cerebral cortex and basal ganglia; (8) neonatal jaundice, occasionally lasting many

weeks; (9) hepatosplenomegaly, which occasionally may last for many months; (10) interstitial pneumonitis, rare (?) (1 case); (11) xanthochromia, moderate round cell pleocytosis and high protein content of the cerebrospinal fluid, presence of Toxoplasma in smears; (12) occasional anemia and leukopenia; (13) recovery of toxoplasmas from the blood or cerebrospinal fluid by inoculation of mice and rabbits intracerebrally and intraperitoneally, and (14) demonstration of neutralizing antibodies to Toxoplasma in the blood.

In this phase the infant may die within a few days after birth or within the first few months of life. Of the aforementioned features, the outstanding clinical findings are the chorioretinitis, the intracerebral calcification, the convulsions and the hydrocephalus.

If the child survives, the picture is modified. It is characterized by (1) healed or inactive chorioretinitis; (2) reduced vision; (3) strabismus, nystagmus and microphthalmos; (4) persisting intracerebral calcification; (5) continuance or late appearance of generalized convulsive seizures or petit mal attacks; (6) chronic hydrocephalus; (7) retardation of speech development, and (8) mental deficiency, usually mild.

In this phase, the children can apparently live on for an indefinite period, and perhaps reach adult life. It is quite probable that such cases of infantile toxoplasmic encephalomyelitis might be mistakenly diagnosed as instances of congenital malformation of the brain, birth injury, epilepsy, congenital hydrocephalus, etc. Children in these categories who show focal chorioretinitis and intracerebral calcification should be investigated for the possibility of toxoplasmosis.

Other conditions which occur during the same age periods and which must be distinguished from this disease are tuberous sclerosis, the cerebromacular degenerations and brain tumor. The tumor-like nodules in the retina in tuberous sclerosis and the single, characteristic, macular lesion in the cerebromacular degenerations can be distinguished by inspection from the multiple areas of focal chorioretinitis of toxoplasmosis. The occurrence of intracerebral calcification would tend to rule out cerebromacular degeneration, but does not distinguish toxoplasmosis from tuberous sclerosis, in which such intracerebral calcification may occur. In general, calcification appears much earlier in toxoplasmosis. The diagnosis of intracranial tumor may be suggested in instances of toxoplasmosis on the basis of the intracranial calcification and the signs of increased intracranial pressure secondary to the hydrocephalus. The presence of ocular lesions, the fact that the calcific shadows are usually multiple and widespread and the pneumencephalographic findings would tend to rule out tumor. The ultimate stabilization of the clinical picture without further progression would help to confirm this.

The serologic test for neutralizing antibodies to Toxoplasma should be carried out in every case in which the possibility of toxoplasmosis

is considered. The data are as yet insufficient to permit complete evaluation of the significance of the test in diagnosis. It seems definite that a more clearcut serologic test is needed to permit one to diagnose correctly cases in which many of the cardinal clinical signs may be missing. Further, a negative result would not, as yet, permit one to rule out the possibility of toxoplasmic infection. It may be said, however, that in the presence of a suggestive history and of striking signs, as previously outlined, a positive serologic result is corroborative.

SUMMARY

A review of the symptoms in 9 cases of infantile, or congenital, toxoplasmic encephalomyelitis recognized at necropsy permitted the formulation of a clinical picture of the disease. The children all died during infancy, usually in the early weeks or months of life, in the acute or subacute stage. The outstanding feature of the syndrome was the concomitant occurrence in infants at or soon after birth of striking ocular lesions and neurologic symptoms and signs. The ocular signs consisted of multiple focal, bilateral areas of chorioretinitis, almost invariably involving the macula, with less constant microphthalmos, nystagmus and ocular palsies. The neurologic findings included convulsions, hydrocephalus and, as the most striking sign, multiple foci of intracerebral calcification.

On this basis, the first 6 clinically identified cases have been diagnosed and are reported here. In the majority of these the patients are children who have survived beyond infancy, indicating that, contrary to our previous experience, the infection is not uniformly fatal and may become chronic, healed or latent. An analysis of the findings in these 6 cases reveals that at this stage the clinical picture consists chiefly of the residual effects of the lesions occurring in the acute or the subacute stage. In these older children the outstanding symptom is usually diminution in vision due to the effects of multiple foci of healed chorioretinitis, which are readily identifiable ophthalmoscopically. Strabismus, microphthalmos and minor congenital ocular defects may also be present. Generalized convulsions or petit mal attacks may persist or later make their appearance. Internal hydrocephalus may become chronic and progressive. Foci of intracerebral calcification persist and may at first increase in number and size. Retardation in the development of speech and minor degrees of mental deficiency occur.

The intrauterine inception of the disease in many, if not all, of these patients is stressed. The fact that these children often survive into the juvenile period would make it desirable to refer to this form of toxoplasmosis as infantile, or congenital, toxoplasmic encephalomyelitis to distinguish it from toxoplasmosis which may be acquired during the juvenile

period and in adult life. These forms might be termed juvenile and adult acquired toxoplasmosis respectively. It may be that a type of acquired infantile toxoplasmosis exists.

Infantile, or congenital, toxoplasmic encephalomyelitis is evidently not a rare disease. It is believed that many cases may have been erroneously classified as instances of congenital malformation of the brain, cerebral birth injury, epilepsy, congenital hydrocephalus, etc. The identification of additional cases may yield some knowledge as to the epidemiology of the disease. In any event, the present indications are that the infection is widespread in the United States, and cases have been encountered in South America and Europe as well. Various mammals, and perhaps birds, are probably the animal reservoirs of the infection, but the mode of transmission to man is not yet known.

The use and limitations of a serologic method as a diagnostic aid are discussed.

Dr. Louis Casamajor placed at our disposal the clinical facilities of the Child Neurology service of the Neurological Institute, and Dr. Rustin McIntosh, of Babies Hospital, furnished us with the clinical material in case 2. Dr. Phillips Thygeson, of the Institute of Ophthalmology, gave advice and assistance; Dr. Ferdinand L. P. Koch's studies of the fundi were invaluable in this investigation, and Dr. Cornelius G. Dyke and Dr. John Caffey advised in the roentgenographic studies.

ACUTE AND SUBACUTE TOXIC MYELOPATHIES FOLLOWING THERAPY WITH ARSPHENAMINES

BEN W. LICHTENSTEIN, M.D.
CHICAGO

The reactions following the treatment of syphilis with arsenical preparations may be mild or severe. To the mild group belong the occasional attacks of headache, vomiting or diarrhea and the so-called nitritoid crisis, characterized by dyspnea, syncope, cyanosis and low blood pressure. Whereas these mild reactions may occur immediately after the administration of an arsenical preparation, the more severe reactions, involving the nervous system (hemorrhagic encephalitis), the blood-forming organs (aplastic anemia), the liver (acute yellow atrophy) and the skin (exfoliative dermatitis), are usually late effects. In the reports of the Salvarsan Committee of the Medical Research Council,[1] only hemorrhagic encephalitis is listed under the heading "effects involving the nervous system." It should be emphasized, however, that the brain is not the sole portion of the nervous system harmfully affected by the arsphenamines and that serious alterations occur in the spinal cord and in the peripheral nerves as well.

The polyneuritis following administration of arsphenamine is similar to the arsenical neuritis from other sources and most commonly occurs four to seven weeks after therapy has been stopped because of the development of dermatitis (Beeson[2]). In some instances, however, the polyneuritis may develop without any cutaneous complication preceding it. Whereas the changes in the brain complicating arsphenamine therapy are as a rule constant—in the nature of so-called hemorrhagic encephalitis—the alterations in the spinal cord are so pleomorphic that superficially at least every case appears to be different. In reviewing the pathologic changes in several instances, however, a thread of similarity can be traced from one to another. Intoxication may produce pathologic alterations in an organ in two ways: first, by direct action

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Read before the Chicago Neurological Society, Feb. 19, 1942.

From the Illinois Neuropsychiatric Institute; the Department of Neurology and Neurological Surgery, University of Illinois, and the Cook County Hospital.

1. Reports of the Salvarsan Committee: II. Toxic Effects Following the Employment of Arsenobenzol Compounds, Medical Research Council, Special Report Series, no. 66, London, His Majesty's Stationery Office, 1922.

2. Beeson, B. B.: Polyneuritis Plus Dermatitis Exfoliativa Following Neo-Arsphenamine, Arch. Dermat. & Syph. **2**:337 (Sept.) 1920.

on the parenchyma, and, second, by affecting its nutrition through action on the blood or the nutrient blood vessels. In many instances a combination of nutritive (vascular) and parenchymatous changes occurs.

It is generally agreed that the changes in the brain following therapy with the arsphenamines result from widespread damage to the smaller blood vessels. As a complication of this vascular alteration, one usually observes perivascular ring-shaped hemorrhages, producing the classic picture of hemorrhagic encephalitis. In many instances the alterations in the blood vessels result in areas of perivascular necrosis, beyond which an area of hemorrhage may or may not be present. The two processes —ring hemorrhages and perivascular areas of necrosis—may be independent of each other. In sharp contrast to the changes in the brain, the classic alterations in the spinal cord following therapy with the arsphenamines result directly from the action of the drug on the parenchyma. In some cases the pathologic process extends into the bulb, and in rare instances changes similar to those occurring in the brain in classic instances of hemorrhagic encephalitis are noted. Frequently the alterations resulting from vascular involvement are coupled with those resulting from direct action of the drug on the parenchyma. In most cases the changes in the spinal cord are so different from the classic changes seen in the brain after administration of arsenical drugs that doubt as to the pathogenic relationship between the action of the drug and the alterations arises. It is for this reason that I report a study of my case and a review of similar cases recorded in the literature. Glaser, Imerman and Imerman [3] pointed out that similar reactions occur also in cases of nonsyphilitic disease and that they are apparently unrelated to the age and sex of the patient, the quantity of the drug administered, the number of injections given or the toxicity of the drug.

REPORT OF A CASE

History.—F. B., a white man aged 61, a lithographer, was admitted to the medical service of Dr. S. Strauss at the Cook County Hospital on June 20, 1941, complaining of pain and weakness in the lower extremities. Through Dr. L. A. Juhnke, the patient's family physician, and Dr. Peter Bassoe, the consulting neurologist, important data became available.

During the course of an antisyphilis campaign, in which every one in the shop in which he worked had a blood test, the patient was discovered to have a positive Wassermann reaction. Because of this he went to his family physician and asked to be treated for syphilis. On reexamination, a positive Kahn reaction of the blood was obtained. Because the patient was symptom free and over 60 years of age, his physician was reluctant to subject him to antisyphilitic treatment, but the patient insisted. After consultation with several other physicians, an agreement

3. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamine, Am. J. M. Sc. **189**:64, 1935.

was reached that some antisyphilitic treatment should be given, and small doses of neoarsphenamine and a bismuth compound were recommended. On questioning, it was learned that the patient had a chancre forty years before (at the age of 21), which was treated with mercury and potassium iodide and that one year ago he had suffered from an attack of "glandular fever."

Antisyphilitic treatment was begun on Feb. 15, 1941, the patient receiving 0.3 Gm. of neoarsphenamine intravenously twice a week. This was followed by injections of 0.1 Gm. of thio-bismol intramuscularly twice a week. After the third dose of thio-bismol the patient began to complain of shooting pains in the buttocks and legs, tingling in the feet and difficulty with micturition. Spinal puncture was

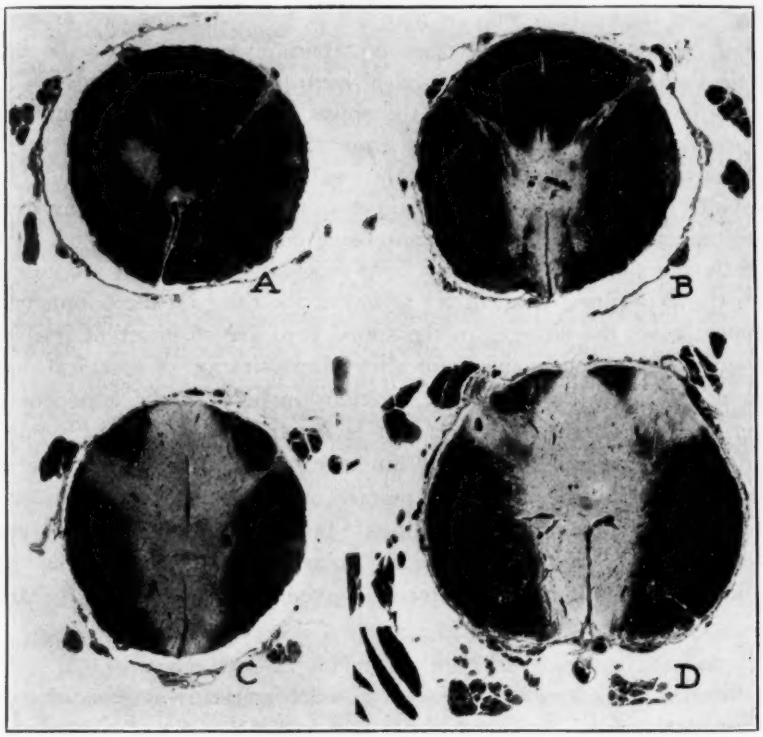

Fig. 1.—Photomicrographs of sections through various levels of the spinal cord, showing the distribution of the demyelinated areas. Weil stain, counterstained by Van Gieson's method.

performed on May 1; the fluid gave negative reactions to the Kahn and Lange tests; the cell count was 3 per cubic millimeter and the test for globulin was negative. Neurologic examination on May 8 gave negative results except for absence of the achilles reflex on the left side and a diminished patellar reflex on the right. The Romberg sign was absent. A diagnosis of incipient tabes dorsalis was suggested and tryparsamide recommended. Six injections of tryparsamide were administered, but the sensory disturbances increased in severity and weakness in the lower extremities began to develop. In this condition the patient was admitted to the Cook County Hospital. He stated that his appetite was poor, that

he had lost 30 pounds (13.6 Kg.) in weight and that during the past three weeks his legs had become progressively weaker. During the past two weeks he had been unable to sit up.

Examination.—On admission to the hospital his temperature was 98 F., his pulse rate 120, his respiratory rate 24 and his blood pressure 126 systolic and 84 diastolic. Physical examination of his chest and abdomen revealed no abnormalities. His pupils did not respond to light, but they reacted well on convergence. The patellar reflex was more active on the left side than on the right; position sense was absent in the toes, and a Babinski sign was elicited bilaterally. Spinal puncture on the day of admission yielded clear fluid under normal pressure, with no cells and a negative Pandy reaction. It was the intern's impression that the case was one of syphilis of the central nervous system, and arsenical poisoning was considered as an alternative diagnosis. The muscular weakness extended upward, and when I saw him on June 24 he breathed with difficulty. Respiration was diaphragmatic in type; there were pronounced atrophy of the interosseous

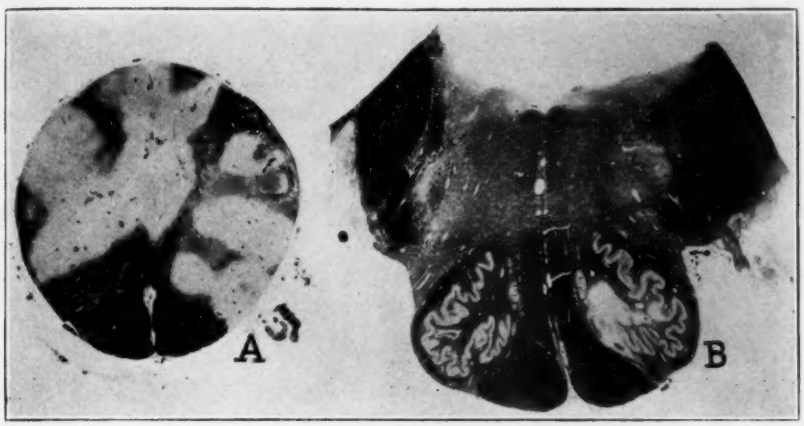

Fig. 2.—Photomicrographs of sections through the medulla oblongata, showing the areas of demyelination. Weil's stain.

muscles of both hands and weakness of the muscles of both forearms. In addition, there was extreme flaccid paraplegia inferior, with absence of the patellar and the achilles reflexes. Palpation of the lower extremities elicited pain, and examination with cotton and pinprick revealed irregular areas of hypesthesia and hyperesthesia. It was my impression that the patient showed evidence of involvement of the peripheral nerves and the spinal cord and that since the disorder came on after medication, the possibility that arsenical intoxication was the cause was to be considered.

Course of Illness.—The patient was given sodium thiosulfate intravenously and was transferred to the contagious disease hospital, where he was placed in a Drinker respirator. While in the respirator, his temperature rose to 100 F. His mind was clear, and he asked about his family. Difficulty in swallowing developed, and he died on June 27.

Necropsy.—The anatomic diagnosis was postarsenical toxic encephalomyelopathy and neuritis; focal bronchopneumonia of the lower lobe of the right lung; paren-

chymatous degeneration of the liver and kidneys; infectious softening of the spleen, and benign hyperplasia of the prostate gland.

Gross Observations: At necropsy, the decreased firmness of the lower thoracic and upper lumbar portions of the spinal cord was striking. After fixation in a 4 per cent concentration of solution of formaldehyde U. S. P., the brain was cut

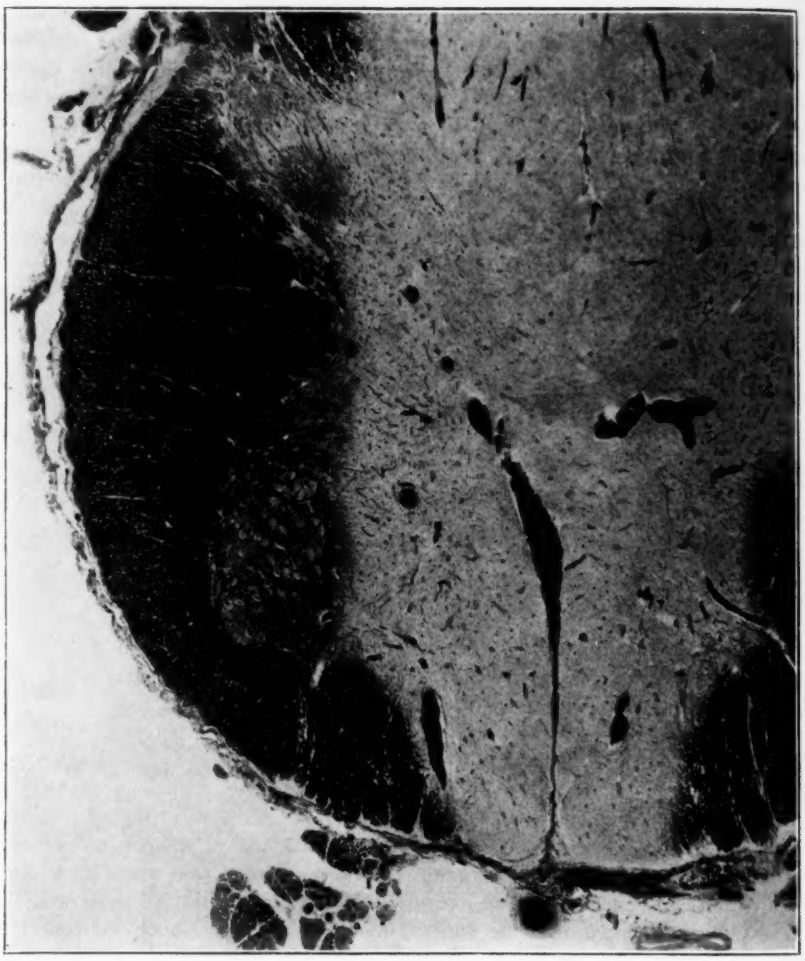

Fig. 3.—Low power photomicrograph of a section taken from the lumbar portion of the spinal cord, showing the sharpness of the line of demyelination through both the gray and the white substance. Weil's stain, counterstained by Van Gieson's method.

in coronal slices and the spinal cord sectioned transversely at numerous levels. Striking gross anatomic changes were observed in the medulla oblongata and in the thoracic and lumbar portions of the spinal cord. In the lumbar portion a band of whitish discoloration, about 4 mm. in width, extended from the anterior aspect of the spinal cord to the pia mater posteriorly. This band involved the median

portions of the anterior columns, the central gray substance and the adjacent portions of the anterior and posterior horns and the dorsal columns. Because of the discoloration, this band stood out in sharp contrast to the unaffected lateral columns. At higher levels the zone of discoloration became more and more narrow, but its central localization was constant. In the upper thoracic and in the lower cervical segments only focal areas of discoloration were seen. Similar whitish patches were observed in the medulla oblongata. At the level of the inferior olive, a patch occurred in one of the folia of the olivary body on one side, and at the level just above the decussation of the pyramids irregular, confluent areas of discoloration were seen throughout the cross section. Careful examination of the cerebellum, pons, midbrain and forebrain failed to reveal similar changes.

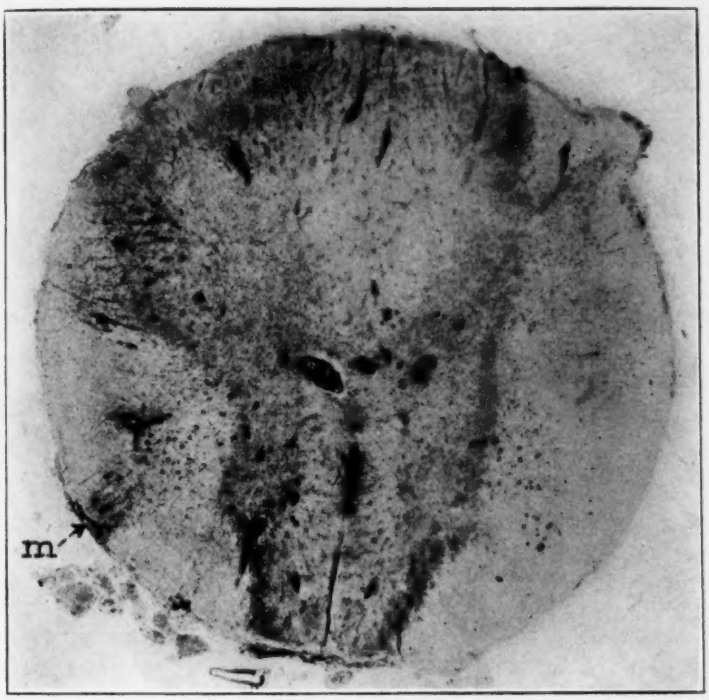

Fig. 4.—Low power photomicrograph of a section through the lumbar portion of the cord, showing the increased cellularity in the demyelinated areas, the perivascular infiltrations and the focal leptomeningitis (*m*). Toluidine blue.

Microscopic Observations: Sections for detailed microscopic study from different portions of the brain and the spinal cord and a portion of the external tibial nerve were embedded in pyroxylin and in paraffin. These sections were stained and impregnated according to various methods. Frozen sections from various portions of the nervous system were stained with oil red O for fat.

Spinal cord and brain: In preparations stained for myelin sheaths, the areas which were described as appearing white in the gross specimen were seen to be demyelinated (figs. 1 and 2). In the spinal cord, the area of demyelination was most extensive in the lower lumbar segments (fig. 1 *D*), where, centering on the central

gray substance, it extended posteriorly to the pia mater and anteriorly to involve the anterior median columns and the adjacent portions of the anterior horns of the gray matter. The zone of demyelination extends as a Y-shaped area to include the posterior horns and the zones where the posterior roots entered. In the areas so affected the demyelination was complete. Above and below the areas of maximum involvement the areas of demyelination gradually decreased in extent. In the middle and lower thoracic segments (fig. 1 *B* and *C*) the distribution of the zone of demyelination was, on the whole, similar to that in the lumbar region. At these levels the zones where the posterior roots entered the spinal cord and the anterior median columns were also affected. At an upper thoracic level (fig. 1 *A*) a focal

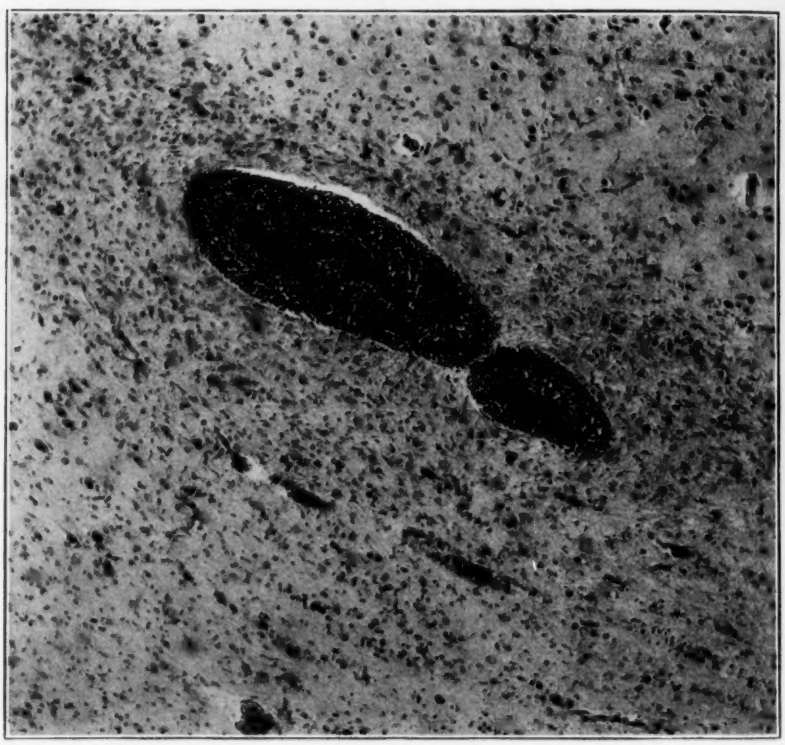

Fig. 5.—High power photomicrograph of a section through the right frontal lobe of the brain, showing marked perivascular infiltrations of lymphocytes and plasma cells. × 93; cresyl violet.

area of demyelination was seen in the lateral limiting zone on one side. In the brain stem the areas of demyelination were limited to the medulla oblongata (fig. 2). In a section at the level of the inferior olivary body (fig. 2 *B*) a focus of demyelination was seen to involve the ventromedial portion of the latter structure, and in a section just above the decussation of the pyramids (fig. 2 *A*) irregular, focal and confluent patches of demyelination involved approximately two thirds of the entire cross section. No areas of demyelination were observed in the midbrain or the forebrain. In the greater majority of the sections studied the diseased areas were completely devoid of myelin, but at some levels, such as in the medulla

oblongata (fig. 2 *A*), areas completely demyelinated bordered on pale areas in which the loss of the myelin was incomplete. The myelin was affected in both the gray and the white substance indiscriminately, and the disease was not restricted to specific nerve bundles or fiber tracts (fig. 3). At some levels unaffected nerve fibers arising from large motor ganglion cells in the anterior horns were seen passing through the demyelinated anterior columns, but in most places the intramedullary continuations of the motor roots were as thoroughly affected as the surrounding tissues.

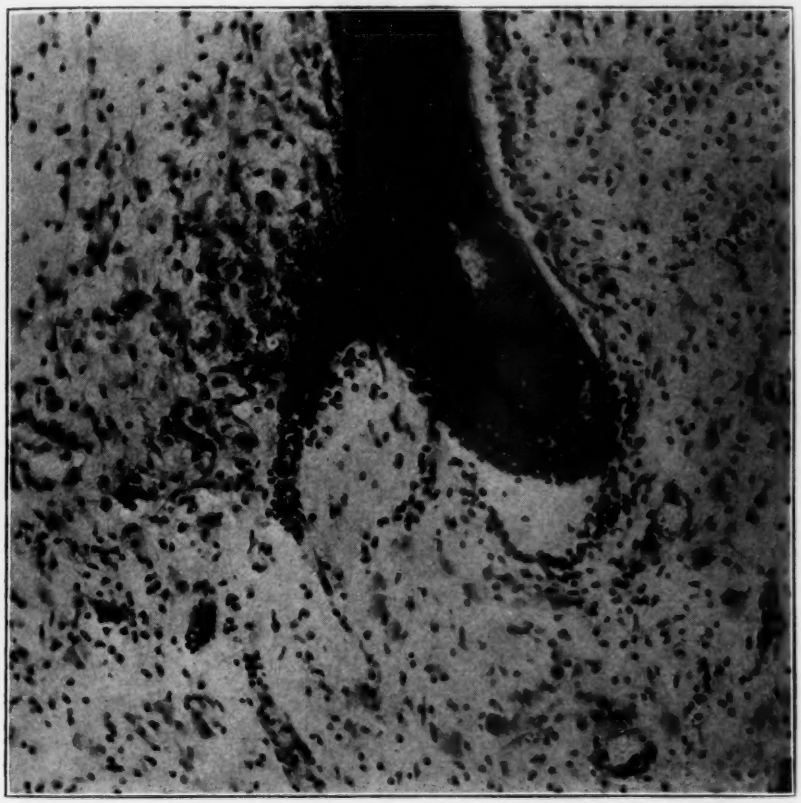

Fig. 6.—High power photomicrograph of a portion of the field seen in figure 4, showing the dense perivascular round cell infiltrations and the increased cellularity of the subjacent spinal cord substance (see text for details). × 190; toluidine blue.

In frozen sections stained with oil red O, the demyelinated areas were heavily laden with fat-filled, compound granular corpuscles (histiocytes). An unusually heavy concentration of these cells was seen in the perivascular spaces and at the border separating the diseased from the healthy areas.

The areas which were demyelinated in preparations stained for myelin proved to be the site of greatly increased cellularity when examined in Nissl preparations (toluidine blue and cresyl violet; fig. 4). This much increased cellularity resolved itself into two components, namely, heavy perivascular infiltrations with lympho-

cytes and plasma cells and a very great increase in the number of glia cells. In the medulla oblongata and in the spinal cord the perivascular infiltrations were, for the most part, restricted to the areas of demyelination, but in the brain, as in the subcortical substance of the right frontal lobe, for example (fig. 5), foci of perivascular cuffing with lymphocytes and plasma cells were seen unassociated with areas of demyelination. The blood vessels (both arteries and veins) were everywhere patent; no thrombi were observed, and the lining endothelium was not

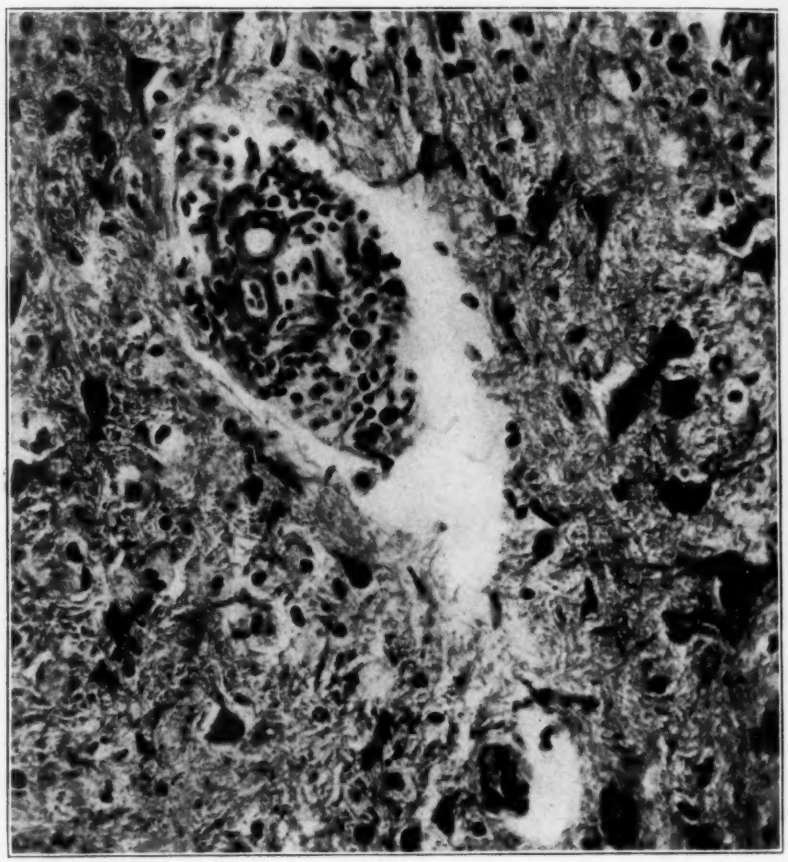

Fig. 7.—High power photomicrograph of a heavily infiltrated area in the spinal cord, showing the perivascular accumulations of lymphocytes, plasma cells and gitter cells and the large numbers of protoplasmic astrocytes in the adjacent parenchyma of the spinal cord. × 338; Achucárro's tannin-silver stain, Hortega's fourth variant.

proliferated. In many places, however, the infiltrations with lymphocytes and plasma cells were not restricted to the Virchow-Robin spaces but permeated the media and the adventitia of the smaller arterioles as well.

The increase in the number of glia cells, in sharp contrast to the perivascular infiltrations, was limited to the areas of demyelination. This increased cellularity

was most pronounced about the infiltrated blood vessels (fig. 6) and at the junction of the demyelinated and the healthy areas. For the most part, these cells consisted of fat-filled histiocytes, as shown so well in oil red O preparations. Scattered among these macrophages, more conspicuous in some places than others, were large protoplasmic astrocytes (fig. 7).

Comparative cytoarchitectonic studies of many levels in the spinal cord failed to show any decrease in the number of ganglion cells. On the whole, little difference could be seen between the nerve cells in the healthy areas and those in

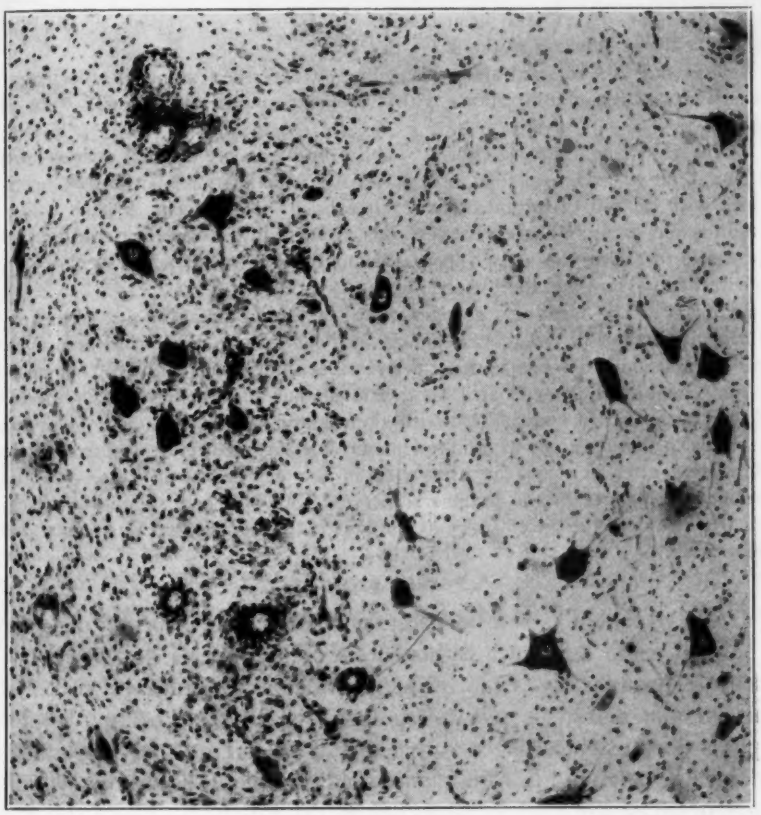

Fig. 8.—High power photomicrograph through an anterior horn of the spinal cord in the lumbar region. Compare the heavily infiltrated area at the left (demyelinated in myelin-stained preparations) with the normal area at the right. Observe the well preserved ganglion cells in both fields. × 93; toluidine blue.

the demyelinated areas (fig. 8). Large motor ganglion cells in the midst of dense accumulations of fat-laden histiocytes and protoplasmic astrocytes and bordering on heavily infiltrated perivascular spaces were seen to have well preserved cell bodies and processes. Their nuclei and nucleoli were distinct, and their cytoplasm contained ample quantities of heavily clumped tigroid substance. Occasional ganglion cells were seen with an increased amount of lipoid material, but these were far in the minority. Sections impregnated according to Penfield's method for microglia

failed to reveal typical rod-shaped microglial elements. Many transverse and longitudinal sections impregnated with silver according to the methods of Bielschowsky, Bodian and Davenport failed to show any significant alterations in the nerve fibers, the ganglion cells or their axons and dendrites. Even in severely demyelinated areas fine neurofibrils could be seen coursing within the cytoplasm of the nerve cells.

Nerve roots: In preparations stained for myelin sheaths many of the posterior roots were demyelinated, and some of the anterior roots were similarly affected, but to a far less extent. At some levels, the zones where the posterior roots entered the spinal cord were observed to be the site of dense perivascular infiltrations with lymphocytes and plasma cells. In Bodian preparations no significant changes could be observed in the nerve fibers.

Leptomeninges: In focal areas, particularly where the leptomeninx bordered on diseased areas, dense infiltrations with lymphocytes and plasma cells were seen (fig. 4 *M*).

Peripheral nerve (external tibial): Unfortunately, only a small portion of one peripheral nerve was available for microscopic examination. In frozen sections stained with oil red O for fat, definite alterations in the myelin sheaths could be seen in some areas. These changes consisted of diffuse swelling and granular appearance of the myelin and an increased affinity for the oil red O similar to that of neutral fat. Here and there were single gitter cells.

Summary: The histologic changes were: extensive areas of demyelination in the central portions of the thoracolumbar segments of the spinal cord and of focal areas in the medulla oblongata; dense perivascular infiltrations with lymphocytes and plasma cells in the demyelinated areas and similar infiltrations in the forebrain and in the spinal cord unassociated with alterations in the parenchyma; focal leptomeningitis in those regions where the leptomeninx bordered on demyelinated tissue; proliferative alterations in the astrocytes in the demyelinated areas, and slight degenerative changes in the peripheral nerves. Striking and significant observations were complete absence of any foci of softening, necrosis or signs of secondary degeneration.

PATHOGENESIS

I believe that it is safe to presume that there will be no unanimity of opinion as to the exact pathogenesis of the lesions described. The absence of proliferative endarteritis, gummas and changes in the elastic tunic of the arterioles speaks against the changes being syphilitic. Syphilis does produce degeneration of the myelin and perivascular and leptomeningeal round cell infiltration, but I strongly doubt the syphilitic origin of all of the changes observed in my case.

A second pathogenic possibility is the Jarisch-Herxheimer reaction, or therapeutic shock. In late syphilis this is usually manifested by acute inflammatory reaction in focal areas and by a general system response as well. Such a possibility could be better entertained in Newmark's [4] case, in which the numbness and weakness of the legs came on two days after a single intramuscular injection of neoarsphenamine, than in my case, in which ten intravenous injections of neoarsphenamine were given. That such a myelopathy may occur after the intravenous administration

4. Newmark, L.: Softening of the Spinal Cord in a Syphilitic After an Injection of Salvarsan, Am. J. M. Sc. **144**:849, 1912.

of neoarsphenamine without the presence of syphilitic infection is evidenced by the report of Glaser, Imerman and Imerman,[3] in which retention of urine, ascending paralysis and sensory disturbances occurred after treatment of Vincent's infection of the throat. I believe that the arsenic was the toxic factor in my case and the precipitating factor in the neuropathologic changes. Another diagnosis suggested in this case is disseminated meningoencephalomyelitis of infectious origin (type of infection unknown). Multiple sclerosis would be a probable diagnosis were it not for the age of the patient.

Since the symptoms began after the administration of thio-bismol and became worse with the administration of tryparsamide, some observers may suggest these two drugs as the inciting agents in the disease.

PATHOLOGY

From the histologic observations presented, it is evident that one is dealing with a disorder affecting the brain, the spinal cord, the nerve roots and the peripheral nerves. Whereas changes in the peripheral nerves were degenerative, no such simple statement can be made about the alterations in the central nervous system, which many observers would consider as either inflammatory or degenerative or both. It is rather difficult to discuss the pathology in the sense of these two terms, however, for there is no unanimity of opinion, at least among neuropathologists, as to just what constitutes inflammation. According to Lubarsch, inflammation is a combination of exudate, proliferative, and degenerative changes. It is well known that not all these three components may be present to an equal degree, and to many observers one of the exudative features (perivascular infiltration) is the diagnostic component of the inflammatory process.

The perivascular infiltrations may be looked on as a reaction on the part of the organism to a noxious agent. The intensity of the reaction —determined by the number and type of infiltrating cells—is determined to a great extent by the local resistance or sensitivity of a given tissue to a particular toxin. This organ immunity or sensitivity is most important, for it determines what organ or system of organs will be affected in a generalized systemic intoxication. In some instances of neoarsphenamine intoxication, for example, the fatal disorder is localized in the liver and the nervous system is spared. In other instances, as in my case, the conditions are reversed. A second factor is the concentration of the noxious material to which the organ is exposed. It appears, in some instances at least, that there is a direct relationship between the intensity of the reaction and the degree of concentration of toxic substance. In the case reported, the perivascular infiltrations, although pronounced in the demyelinated area, were also observed in

areas showing no sign of degeneration. Some observers may interpret the infiltrations of lymphocytes and plasma cells in the heavily demyelinated areas as a "symptomatic" response to degeneration, but I believe it is an independent process indicating a type of response to a noxious agent—in this case, arsenic. It is well known that in secondary degeneration, despite the severe alterations in the parenchyma, with destruction of both axons and myelin, perivascular infiltrations with inflammatory cells do not occur as a rule.

The second important component of the pathologic process was the degeneration of the myelin. Histopathologically, the cellular alterations were not different from those seen in other degenerative disorders—such as multiple sclerosis or Friedreich's ataxia. Since the disease was subacute and widespread, large numbers of fat-laden histiocytes were observed in certain portions of the nervous system. The degeneration was not restricted to specific nerve bundles or fiber tracts, as in secondary degeneration, but involved both the gray and the white matter in an irregular manner. In this respect the disorder resembled the chronic degenerative disorder of the nervous system classified pathologically as multiple sclerosis. As in multiple sclerosis, no degenerative changes in the macroglia were observed. On the contrary, large numbers of protoplasmic astrocytes were seen throughout the demyelinated areas. As could be expected from the subacute course of the illness, no striking foci of "gliosis" or glial scars were seen, all of the astrocytes still being cytoplasmic, not fibrillary. The macroglia was activated either by stimulation of the harmful substance—arsenic—that destroyed the myelin or, more likely, by the degenerative process itself, for the role of the glia is, like that of other supportive cells in the organism, namely, the fibrocytes, to heal by scar formation. The axons and dendrites were practically unaffected. The ganglion cells, too, showed minimal alterations, and those in the demyelinated, infiltrated areas showed little difference from those in the adjacent unaffected areas.

The cellular reactions in the leptomeninx may be considered as a "symptomatic" response, for they were sharply delimited to those areas where demyelinated foci bordered on the leptomeninx, but, like the perivascular infiltrations, I am inclined to consider them as a response to the toxic agent itself.

Hassin [5] classified disseminated lesions of the central nervous system as inflammatory (encephalomyelitis), acute and subacute degenerative (multiple degenerative softenings), chronic degenerative (multiple

5. Hassin, G. B.: Disseminated Encephalomyelitis (Meningoencephalomyeloradiculitis) Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **40**:1111 (Dec.) 1938.

sclerosis) and neoplastic (multiple tumors). Such a classification is excellent, but, as in all other attempts at classification, there are, unfortunately, limitations, and frequently cases are encountered which do not easily fall into such subgroups. Hassin [6] stated: "In the usual inflammatory, infectious type of encephalomyelitis, the phenomena are inflammatory and overshadow the degenerative changes, which generally are meager." In the encephalomyelitis of Heine-Medin disease, however, ganglion cell degeneration is a classic feature, and in the encephalomyelitis complicating measles destruction of the myelin, and in some instances of the axis-cylinders as well, is extensive, but probably Hassin did not consider measles and infantile paralysis as usual infectious diseases. He [6] included the acute and subacute degenerative diseases under the heading of multiple degenerative softening, adding that in this disease "large patches of demyelination are numerous in the pons and elsewhere in the brain but sparse in the medulla [oblongata] and the spinal cord." In the case presented, it will be recalled that the patches of demyelination were restricted to the medulla oblongata and the spinal cord.

Neuropathologic discussions are made even more complicated by the lack of universal agreement as to the meaning of malacia (softening). If one considers the mere presence of large numbers of gitter cells as diagnostic of softening, then one is forced to consider subacute combined degeneration of the spinal cord and many of the foci in multiple sclerosis and in other diseases as areas of softening. Such a criterion for softening can only lead to confusion. I believe that the word softening (malacia) should be reserved for the process in which there is destruction of the myelin, axis-cylinders (ganglion cells) and the macroglia (astrocytes and oligodendrocytes), with preservation of the mesodermal elements (microglia, blood vessels and meninges), the latter playing an active role in attempts at repair. In necrosis, on the other hand, there is massive death of all of the cellular elements in the focus affected—myelin, axis-cylinders, macroglia, microglia and blood vessels. If one considers the alterations of the central nervous system under three headings—degeneration, malacia and necrosis—much confusion will be avoided. Since malacia and necrosis have been described, it is only the term degeneration that needs clarification. This may be defined as a breaking down of the myelin and/or the axis-cylinders and/or ganglion cells with progressive changes in the astrocytes. Multiple sclerosis is a classic example of the chronic degenerative disorder. In that pathologic entity, there is widespread destruction of the myelin asso-

6. Hassin, G. B.: Pathologic Features of Multiple Sclerosis and Allied Conditions, Arch. Neurol. & Psychiat. **38**:713 (Oct.) 1937.

ciated with activation of the astrocytes, which finally leads to glial scar formation.

Cases of acute (Grinker and Bassoe [7]) and subacute (Symonds [8]) disease characterized by areas of demyelination with relative preservation of axis-cylinders and infiltration with round and glial cells have been reported. In many instances, especially in the cases in which infiltrations with lymphocytes and plasma cells are few or absent, the pathologic picture has been designated acute multiple sclerosis. The same histologic picture has been produced in the central nervous system of animals by the experimental administration of various toxic agents. What is of even more significance is that in many cases such foci coexisted with areas of softening. In rare instances all the types of changes possible —degeneration, malacia, necrosis and inflammatory phenomena—were encountered, the nature of the reaction depending probably on the dose of the toxic material administered, its mode of administration, the age and physical condition of the experimental animal and the local sensitivity of the nervous system to the noxious agent. Thus, Lotmar [9] produced changes in the central nervous system of rabbits by the intravenous injection of dysentery toxins. He distinguished two types of reaction: type 1, in which large doses of the inciting agent were used, the pathologic features were hemorrhages, exudate of fibrin and polymorphonuclear leukocytes, thrombosis of the blood vessels, degeneration and vacuolation of the ganglion cells, swelling of the axis-cylinders and ameboid changes in the glia. The astrocytes in this type of reaction did not show proliferative changes. The alterations described were those of malacia and necrosis. In type 2 the astrocytes showed signs of proliferation despite the presence of large numbers of gitter cells. The alterations in type 2 were purely those of degeneration.

Claude [10] produced degeneration in the central nervous system of dogs by the injection of tetanus toxin, and this experiment was repeated by Putnam and his co-workers.[11] In many instances "inflammatory elements" were associated with the degeneration.

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7. Grinker, R. R., and Bassoe, P.: Disseminated Encephalomyelitis, Arch. Neurol. & Psychiat. **25**:723 (April) 1931.

8. Symonds, C. P.: Pathological Anatomy of Disseminated Sclerosis, Brain **47**:36, 1924.

9. Lotmar, F.: Beiträge zur Histologie der akuten Myelitis und Enzephalitis, sowie verwandter Processe, auf Grund von Versuchen mit Dysenterietoxin, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1913, vol. 6, no. 2.

10. Claude, H: Myélite expérimentale subaiguë par intoxication tétanique, Arch. de physiol. norm. et path. **29**:843, 1897.

11. Putnam, T. B.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931.

Ferraro,[12] using cats and monkeys, produced alterations in the central nervous system by the subcutaneous injection of potassium cyanide. A pleomorphic variety of changes was recorded, all of which, however, can be included in the four types of reaction: degeneration, malacia, necrosis and inflammation. In some he observed foci of malacia, and in others, foci of necrosis. In some foci the myelin alone was degenerated, while in other places the degeneration of the myelin was coupled with degeneration of the axis-cylinders. In places, the blood vessels had undergone hyaline degeneration. Acute degenerative changes in the nerve cells were observed. In 2 animals definite inflammatory lesions were observed and Ferraro[12] stated:

> I am at a loss as to an explanation of the inflammatory lesions of the two above-mentioned cases and the chance that the toxic factor may have stirred up a latent infection is a possibility to be kept in mind. On the other hand, it may be possible that a toxic factor by itself can, under particular circumstances, such as a particular form of resistance of the tissue, develop a true inflammatory reaction.

Personally, I am at a loss to know why neuropathologists are so disturbed by inflammatory reactions in so-called degenerative diseases. Inflammation does not imply infection. Infection signifies invasion of the tissues by pathogenic micro-organisms or animal parasites and the results which follow on that invasion. Not all infectious diseases of the central nervous system show an inflammatory response.

To illustrate the pleomorphic reactions of the nervous system to a single intoxicating agent—the arsphenamines—I have analyzed a number of reported cases in which autopsy was performed. These cases illustrate the four classic types of histologic response: degeneration, malacia, necrosis and inflammation (table).

In Fleischmann's[13] case the histologic alterations were degenerative, those of acute cell disease of the ganglion cells in the anterior horns and in Clarke's columns. In my case the changes were degenerative, with particular involvement of the myelin sheaths, the ganglion cells and nerve fibers showing minimal involvement. In Newmark's[4] case foci of degeneration, as well as foci of malacia, were observed. In Oseki's[14] case a poliomyelitic type of inflammation was seen in the anterior horns of the lumbar region, and foci of malacia also were noted. In Chiari's[15] case the foci of malacia were associated with an acute inflammatory

12. Ferraro, A.: Experimental Toxic Encephalomyelopathy, Psychiatric Quart. **7**:267, 1933.

13. Fleischmann, R.: Ueber einen Fall von Landryscher Paralyse bedingt durch Salvarsanintoxication, Ztschr. f. d. ges. Neurol. u. Psychiat. **14**:125, 1913.

14. Oseki, M.: Beitrag zur Kenntnis der Salvarsanschäden des Rückenmarks, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **25**:269, 1924.

15. Chiari, H.: Ueber eine nach Neosalvarsan-Injektionen aufgetretene "Myelitis," Verhandl. d. deutsch. path. Gesellsch. **16**:155, 1913.

Author	Date	Yr. Age,	Sex	History and Onset	Course and Clinical Signs	Pathologic Changes
Fleischmann.....	1913	35	M	Acquired syphilis in June 1911; received mercury by inunction and injection; Jan. 19: 0.5 Gm. neoarsphenamine intravenously; Jan. 31: 0.5 Gm. neoarsphenamine intravenously; Feb. 13: weakness in the legs	Spread of muscular weakness to the back, abdomen and upper extremities; sensation intact; patellar and achilles reflexes absent; weakness of respiratory muscles; death in two weeks	Severe alteration of the ganglion cells in anterior horns and Clarke's column
Present case.....	1942	61	M	Acquired 40 yr. ago; treated with mercury and potassium iodide; positive Wassermann reaction of blood on routine examination 2/15/41; 0.3 Gm. neoarsphenamine twice a week for 10 injections, followed by 0.1 Gm. thio-bismol twice a week; onset of illness after third dose of thio-bismol, with paresthesias in the feet	Shooting pains in buttocks and legs followed by difficulty with sphincter control; muscular weaknes of lower extremities; upward spread of paresis to involve muscles of back and abdomen and those of upper extremities; respiratory paralysis; death in two months	Foci of degeneration in the medulla oblongata and the spinal cord; perivascular and leptomeningeal round cell infiltrations
Newmark.....	1912	23	M	Acquired syphilis in 1908; treated with mercury; June 10, 1911: 0.3 Gm. neoarsphenamine injected in buttock; June 12, 1911: numbness and weakness of the legs	Rapid development of paraplegia inferior, of flaccid type; knee jerks ±; ankle jerks —; complete sphincter paralysis; impaired sensibility below level of navel; bed sores; 0.6 Gm. neoarsphenamine; death from sepsis in two and one-half months	Foci of degeneration; foci of softening; perivascular and leptomeningeal round cell infiltrations
Oseki.....	1924	29	F	Acquired syphilis in 1909; March 4, 1914: (?) Gm. neoarsphenamine; March 5, paresthesias of the feet; retention of urine; weakness of legs	Rapid development of paraplegia inferior; upward spread of paralysis; death from pneumonia in ten days	Poliomyelitic type of inflammation in the anterior horns of the lumbar position of cord; foci of malacia; perivascular and leptomeningeal round cell infiltrations in spinal cord and brain
Chiari.....	1913	27	F	Acquired syphilis in March 1912; June 1: 0.7 Gm. neoarsphenamine intravenously; June 4: 1.2 Gm. neoarsphenamine intravenously; June 7: 1.4 Gm. neoarsphenamine intravenously; scarlatiniform exanthem for nine days; June 13: urinary retention	Sensory disturbances and weakness of lower extremities, followed by rapidly developing total paraplegia inferior; sacral decubitus; death from sepsis in one week	Foci of malacia in 7th to 9th thoracic segments; perivascular infiltrations with polymorphonuclear leukocytes
Scott and Reinhart..	1929	23	M	No history or signs of syphilis; patient requested blood test without giving reason; Kahn reaction of blood strongly positive; 0.9 Gm. neoarsphenamine given intravenously; five days later 0.9 Gm. neoarsphenamine; complained of a cold 8 hr. later but improved; two days later weakness and numbness of feet and ankles	Rapid development of flaccid paralysis of lower extremities, which extended upward; paresthesias in hands, associated with paresis of upper extremities; suppression of deep reflexes; anesthesia to the second rib; distention of urinary bladder; death after two weeks	Malacia; degeneration of blood vessels with perivascular hemorrhages

response, characterized by perivascular polymorphonuclear leukocytic infiltrations, and in the case of Scott and Reinhart [16] the parenchymatous changes were coupled with nutritive alterations, namely, degeneration of the blood vessels and perivascular hemorrhages.

CLINICAL CONSIDERATIONS

Postarsphenamine toxic myelopathy is apparently more common in the male than in the female, and all the reported cases have occurred in adults. In the great majority of the cases, the patients were symptom free prior to the onset of the myelopathy, a positive serologic reaction of the blood for syphilis being the only abnormal finding. The time relationship between the date of onset of the myelopathy and the age of the syphilitic infection varied considerably. In some instances the complicating disorder set in a few years after the acquisition of syphilis, and in the case I studied the chancre was acquired forty years before. The only definite relationship that could be established is that of onset of the symptoms referable to the spinal cord after the administration of the arsphenamine. Whereas in some instances the complicating disorder developed as early as one day after the administration of the drug, in others many weeks elapsed. That there is great individual variation in the sensitivity of the patient to the arsenical preparation is evidenced by the fact that in some instances (Newmark [4] and Oseki [14]) one injection provoked alterations in the spinal cord and in other instances as many as ten injections were given before symptoms developed.

In every instance the presenting symptoms were referable to the lower extremities. In Fleischmann's [13] case the disorder was purely motor, being characterized by flaccid paralysis, while in the majority of instances the initial symptoms were in the sensory sphere (paresthesias) and were soon followed by flaccid paralysis of the lower extremities. In cases of severe involvement urinary retention occurred early, and in cases in which the process had a slow evolution, difficulty with micturition was present for some time before complete urinary retention developed.

The course of the disorder is characterized by an upward march of the motor and sensory disturbances, and it is for this reason that many of the cases were described as instances of Landry's paralysis. The rate of spread of the disorder varied considerably, and two subforms can be recognized—the acute, in which the disorder spread to the medulla, producing death from respiratory paralysis in two weeks (Fleischmann [13]), and the subacute, in which as much as ten weeks elapsed

16. Scott, E., and Reinhart, H. L.: Acute Diffuse Myelitis Following Intravenous Injection of Neoarsphenamine, J. Lab. & Clin. Med. **15**:405, 1929.

between the time of onset and death from respiratory failure. In rare instances, the upward spread of the disorder stops spontaneously, as in the case of Moseley and Callaway,[17] in which after a stormy onset, with flaccid paralysis of the lower extremities, anesthesias and sphincteric disturbances, the spread of the disorder stopped spontaneously and the patient was discharged from the hospital after five months with the trophic ulcers healing. In the instances in which the evolution of the disorder is slow, death may occur from sepsis or pneumonia.

A proper diagnosis is not difficult to make if the possibility of a causal relationship between the symptoms and the medication is kept in mind. In most instances there is no evidence of previous involvement of the nervous system. To some, Landry's paralysis is a favorite diagnosis, for the disorder is flaccid and ascending in type. Most authorities, however, believe that such a term should not be used, for, as Wilson so aptly remarked: "As a technical term, 'Landry's paralysis' lacks precision, aetiological or pathological, and its clinical worth is a little dubious."

A second clinical diagnosis frequently made in cases of postarsphenamine toxic myelopathy is syphilitic myelitis. For many reasons, such a diagnosis is dangerous, for it may urge the clinician to give more antisyphilitic treatment, which may hasten the progress of the disorder. In those instances in which the disorder is limited to the anterior horns and is acute in onset, a clinical diagnosis of acute anterior poliomyelitis is suggested (Oseki [14]; Scott and Reinhart [16]), and in my case in which the onset was gradual, with shooting pains in the legs, difficulty with micturition and loss of the achilles reflex, a diagnosis of tabes dorsalis was suggested. The subsequent course of the disease, which was rapid (flaccid paralysis and ascending anesthesia), however, indicated that the disorder was more serious than tabes.

CONCLUSIONS

1. The arsphenamines may produce changes in the nervous system through the medium of the blood vessels and/or by direct action on the parenchyma.

2. In classic instances of "postarsphenamine encephalitis" the drug affects the blood vessels, and this may result in perivascular areas of necrosis and/or hemorrhage.

3. In classic instances of "postarsphenamine myelitis" the drug affects the parenchyma. The histologic alterations in this disorder are pleomorphic and may be classified as (*a*) degeneration of the ganglion

17. Moseley, V., and Callaway, J. L.: Transverse Diffuse Myelitis of the Spinal Cord Following Intravenous Neoarsphenamine, Am. J. Syph., Gonor. & Ven. Dis. **24**:746, 1940.

cells, the myelin or the nerve fibers, with proliferative changes in the astroglia; (*b*) malacia; (*c*) necrosis, and (*d*) inflammatory phenomena —perivascular and leptomeningeal infiltration of lymphocytes and plasma cells and, rarely, of polymorphonuclear leukocytes.

4. In some instances of "postarsphenamine myelitis" the histologic alterations are similar to those seen in the brain in classic instances, namely, vascular alterations resulting in perivascular hemorrhages.

5. In many instances a combination of various parenchymatous changes with or without vascular phenomena are encountered.

6. The postarsphenamine myelopathy is, as a rule, located in the lower thoracic and the lumbar portion of the spinal cord.

7. The parenchymatous alterations may extend into the brain stem or even higher.

8. Postarsphenamine myelopathy is usually associated with degeneration of the peripheral nerves.

9. The disorder is usually ascending, acute or subacute in course, and death results from respiratory paralysis or sepsis.

10. In nonfatal cases there is evidence of permanent damage to the spinal cord.

11. The disorder is probably the result of sensitivity of the nerve tissues or the vascular bed to the arsenic, and is not modified by the age, sex or physical condition of the patient.

12. The disorder must be differentiated from syphilitic myelitis, the Herxheimer reaction, multiple sclerosis and disseminated encephalomyelitis of unknown origin.

1853 West Polk Street.

DISCUSSION

DR. GEORGE B. HASSIN, Chicago: The changes presented by Dr. Lichtenstein are not unusual and have been described in association with various conditions. In 1938 I (Disseminated Encephalomyelitis [Meningoencephalomyeloradiculitis], ARCH. NEUROL. & PSYCHIAT. **40**:1111 [Dec.] 1938) reported a case in which a similar clinical picture was presented; paraplegia, which became flaccid, was combined with sensory and genitourinary disturbances, gradual upward extension of the process, as in Landry's paralysis, and development of bulbar manifestations, followed by death. There was, however, no evidence of syphilis in the history, and no arsphenamine or other antisyphilitic treatment had been given. Yet the clinical and pathologic features were similar to those described by Dr. Lichtenstein, except that in my case demyelination was pronounced in the medulla. It was not demonstrable in the spinal cord with the Weigert-Pal method, but degenerative changes there were well brought out with toluidine blue. The changes were both degenerative and infiltrative and were present not only in the spinal cord and medulla but in the subcortical areas of the brain, the globus pallidus and the corpus striatum; in addition, there were changes in the meninges and the posterior nerve roots. On the basis of such widespread changes, I made the diagnosis of disseminated encephalomyelitis. I ascribed the changes to some toxic-infectious factor, while Dr. Lichtenstein, in his case, saw the cause of the changes in the direct action of the arsenicals (neoarsphenamine and tryparsamide) on the nerve parenchyma. However, the common pathologic lesions produced by

the arsphenamines are ring hemorrhages. Globus and Ginsburg (Pericapillary Encephalorrhagia Due to Arsphenamine, ARCH. NEUROL. & PSYCHIAT. **30**:1226 [Dec.] 1933) gave an exhaustive review of the literature on this subject but did not mention a single instance in which the changes were like those described by Dr. Lichtenstein. Nor do I know of a case in which a disseminated lesion involving not only the spinal cord and the medulla but also the brain, the meninges, the roots and the peripheral nerves resulted from administration of arsphenamines or tryparsamide. The references from the older literature offered by Dr. Lichtenstein do not pertain to disseminated encephalomyelitis, which was the actual condition in his case. The occurrence of this disease was accidental and had nothing to do with the administration of the arsphenamines or the tryparsamide.

Disseminated lesions of the nervous system could not be produced by arsphenamine experimentally. Weygandt, Jacob and Kafka (*München. med. Wchnschr.* **61**:1608, 1914) tried to produce changes in the central nervous system by injecting neoarsphanamine in monkeys, in the subarachnoid space and intracerebrally. All they produced were proliferative mesodermal alterations similar to those observed in cases of lead encephalopathy, and nothing else. If Dr. Lichtenstein can prove that the histologic changes in his case, which was one of disseminated encephalomyelitis, were due to the action of the arsenicals, his would be a splendid contribution to the science of neuropathology.

DR. PERCIVAL BAILEY, Chicago: I did not hear anything about the olfactory bulbs. Inflammation there might serve to differentiate postarsphenamine intoxication and a virus infection.

DR. JOSEPH A. LUHAN, Chicago: About when did the patient receive the tryparsamide, and what was the relation of its administration to the condition?

DR. ROY R. GRINKER, Chicago: The histologic picture in this case is indistinguishable from that in the case which Dr. Bassoe and I reported.

DR. BEN W. LICHTENSTEIN, Chicago: I stated in my paper that among neuropathologists at least there would be no agreement as to the exact pathogenesis of the lesions in this case. Since changes were present in the brain, the spinal cord, the leptomeninges and the nerve roots, Dr. Hassin suggested a diagnosis of meningoencephalomyeloradiculitis. A diagnosis, however, should be more than a mere listing of the structures involved. My teacher, Dr. R. H. Jaffé, always pointed out the difference between organ pathology and the pathology of disease; many organs may be involved but the clinical symptomatology may be referable to one.

In this case the course was subacute, and the localization of the disease clinically was in the spinal cord. The ascending paralysis and sensory disturbances came on after the administration of arsenical preparations. The literature contains many reports of similar disorders, both acute and subacute. In all the fatal cases, death resulted from respiratory paralysis or sepsis. The involvement of the meninges and the nerve roots was minor as compared with the alterations in the spinal cord. Terminally the disease extended into the bulb. Similar changes could have resulted from intoxications other than arsenic, as I brought out in my discussion of the pathogenesis. There are, as a matter of fact, few diseases in which the microscopic pathology tells the exact nature of the pathogenic agent. Syphilis is identifiable in most instances, as are tuberculosis, leprosy and typhoid. If an organism is not identified, one cannot tell from the histologic preparations the exact nature of the encephalitis, myelitis or meningitis. The changes in my case were degenerative and inflammatory and differed from the classic alterations seen in the brain in this disorder—hemorrhagic encephalitis.

In reply to Dr. Luhan, administration of tryparsamide was begun after the symptoms had developed.

INSULIN SENSITIVITY OF PATIENTS WITH MENTAL DISEASE

FACTORS IN THEIR SERUM AFFECTING ACTION OF INSULIN

MEYER M. HARRIS, M.D.
NEW YORK

Recent advances in endocrinology have disclosed that many factors enter into the regulation of carbohydrate metabolism in the animal organism. Not only the pancreas and its secretion of insulin but the pituitary,[1] the adrenals,[2] the thyroid,[3] the sex glands,[4] the liver[5] and

From the Department of Internal Medicine of the New York State Psychiatric Institute and Hospital.

1. (*a*) Houssay, B. A.; Biassotti, A., and Rietti, C. T.: Action diabetogène de l'extrait anté-hypophysaire, Compt. rend. Soc. de biol. **111**:479, 1932. (*b*) Marks, H. P., in Discussion of Physiological Factors Influencing the Action of Insulin, Proc. Roy. Soc. Med. **29**:663, 1936. (*c*) Russell, J. A.: The Action of Insulin and Anterior Pituitary Extract in Normal and Hypophysectomized Rats, Am. J. Physiol. **124**:774, 1939. (*d*) Flaum, G.: Insulin Sensitivity: Its Possible Relation to the Pituitary Gland, Endocrinology **23**:630, 1938. (*e*) Barnes, B. O., and Regan, J. F.: The Relation of the Anterior Pituitary to Carbohydrate Metabolism, ibid. **17**:522, 1933.

2. (*a*) Corey, E. L., and Britton, S. W.: Carbohydrate Metabolism of Hypophysectomized and Hypophyso-Adrenalectomized Rats, Am. J. Physiol. **118**:15, 1937. (*b*) Britton, S. W., and Silvette, H.: Effects of Corticoadrenal Extracts on Carbohydrate Metabolism, ibid. **100**:701, 1932. (*c*) Zwemer, R. L.: Electrolyte and Sugar Determinations as Indicators of Adrenal Influence, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5, p. 323. (*d*) Katzin, B., and Long, C. N. H.: The Effect of Adrenocortical Hormone on the Liver and Muscle Glycogen of Normal Fasting Mice and Rats, Am. J. Physiol. **123**:113, 1938.

3. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937, p. 43.

4. (*a*) Gulick, M.; Samuels, L. T., and Deuel, H. J., Jr.: The Sexual Variation in Carbohydrate Metabolism: The Effect of Ovariectomy and Theelin Administration on the Glycogen Contents of Rats, J. Biol. Chem. **105**:29, 1934. (*b*) Glen, A., and Eaton, J. C.: Insulin Antagonism, Quart. J. Med. **7**:271, 1938.

5. Cope, O.: The Relation of Pituitary to Liver Glycogen Production and Utilization, J. Physiol. **88**:401, 1937. Soskin, S., and Mirsky, I. A.: Influence of Progressive Toxemic Liver Damage upon the Dextrose Tolerance Curve, Am. J. Physiol. **112**:649, 1935. Soskin, S.; Mirsky, I. A.; Zimmerman, L. M., and Heller, R. C.: Normal Dextrose Tolerance Curves, in the Absence of Insulin, in Hypophysectomized-Depancreatized Dogs, ibid. **114**:648, 1936.

the diet [6] all play a role in the regulation of the metabolism of this dietary constituent. The part played by the various factors has been discussed in some previous publications [7] and in a number of reviews on the subject.[8]

With the complexity of the problem in mind, a study of the insulin sensitivity of a group of patients with mental disease and of the possible presence of substances in their serum which affect the action of insulin is reported.

It has been known for some time that certain conditions render the blood sugar level susceptible to the effect of the injection of small doses of insulin, whereas other conditions produce a state of resistance to insulin. Thus, for example, adrenalectomy [9] or Addison's disease [10] has been found to be accompanied by marked sensitivity, whereas in certain cases of pituitary tumor [11] resistance may be increased. Fernbach,[11a] in 1932, using the test of Csépâi and Ernst, which consists of the intravenous injection of 0.06 unit of insulin per kilogram of body weight and the determination of the blood sugar before and thirty, sixty and one hundred and twenty minutes after the injection, found in a case of Parkinson's syndrome and in certain cases of brain tumor occurring in the posterior fossa that the normal drop in blood sugar, namely, 25 to 35 per cent of the initial level, occurred at the end of

6. (*a*) Himsworth, H. P.: Dietetic Factors Determining the Glucose Tolerance and the Sensitivity to Insulin of Healthy Men, Clin. Sc. **2**:67, 1935. (*b*) Hynd, A., and Rotter, D. C.: Studies on the Metabolism of Animals on Carbohydrate Free Diets, Biochem. J. **25**:457, 1931.

7. Harris, M. M.; Blalock, J. R., and Horwitz, W. A.: Metabolic Studies During Insulin Hypoglycemia Therapy of the Psychoses, Arch. Neurol. & Psychiat. **40**:116 (July) 1938; Further Metabolic Studies Regarding the Effect of Insulin Hypoglycemic Therapy in Mental Patients: Metabolic Changes Accompanying the Glucose Tolerance Test Before and After the Course of Treatment, Psychiatric Quart. **12**:489, 1938; Metabolic Studies of Mental Patients Treated with Insulin Hypoglycemic Shock Treatment: III. Potassium Tolerance Before and After Treatment, ibid. **13**:429, 1939.

8. (*a*) Long, C. N. H.: The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, Medicine **16**:215, 1937. (*b*) Russell, J.: The Relation of the Anterior Pituitary to Carbohydrate Metabolism, Physiol. Rev. **18**: 1, 1938. (*c*) Cori, C. F., and Cori, G. T.: Carbohydrate Metabolism, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 10, p. 151.

9. Corey and Britton.[2a] Britton and Silvette.[2b] Zwemer.[2c] Long.[8a]

10. Soskins, S.: Metabolic Functions of the Endocrine Glands, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 3, p. 543.

11. (*a*) Fernbach, J.: Die Insulinempfindlichkeit beim Gehirnerkrankungen, Ztschr. f. klin. med. **122**:595, 1932. (*b*) Flaum.[1d]

thirty minutes. However, the blood sugar level tended to remain depressed one to two hours after the injection. In the normal subject the blood sugar returns to the initial level within this period. Fernbach [11a] expressed the belief that this disturbance in the process of recovery was probably due to interference with sympathetic pathways which stimulate the secretion of epinephrine, whereby sugar is mobilized from glycogen stores in the liver. It may be stated, however, that animal experiments indicate that while removal of the medullary portion of the adrenal glands may produce some or no decrease in the ability for spontaneous recovery, loss of the cortices of both adrenal glands results in considerable prolongation of the hypoglycemia due to insulin.

Owing to the failure of some patients with glycosuria to respond to insulin, investigators have sought for the possible presence in the blood of these patients of a substance antagonistic to the action of insulin. In 1935 Boller and Uiberrak [12] claimed to have demonstrated the presence of some substance antagonistic to insulin in the blood of such a resistant patient.

De Wesselow and Griffiths [13] claimed that the blood of obese, middle-aged persons with mild diabetes also contained substances antagonistic to insulin. This was demonstrated by injecting the serum of such persons into rabbits previously standardized against an intravenous test dose of insulin. Several hours after the injection of the serum the test dose of insulin was injected intravenously, and the effect on the blood sugar curve was determined. A comparison of this curve indicating the degree of depression of the blood sugar level with the standard curve previously obtained revealed whether substances antagonistic to the action of insulin were present in the serum.

It is apparent from the foregoing discussion that in a consideration of the factors affecting sensitivity to insulin two phases are to be distinguished, namely, the production of hypoglycemia and the recovery from the hypoglycemic state. Frazer and his associates,[14] in their recent publications, pointed out the importance of this consideration in

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12. Boller, R., and Uiberrak, K.: Die Einfluss chronischer und akuter Hyperinsulinisierung auf die alimentäre Hyperglykämie beim Diabetes mellitus, Wien. Arch. f. inn. Med. **27**:75, 1935.

13. de Wesselow, O. L. V., and Griffiths, W. J.: On the Possible Role of the Anterior Pituitary in Human Diabetes, Lancet **1**:991, 1936.

14. Frazer, R.; Albright, F., and Smith, P. H.: Value of Glucose Tolerance Test, the Insulin Tolerance Test and Glucose-Insulin Tolerance Test in Diagnosis of Endocrinological Disorders of Glucose Metabolism, J. Clin. Endocrinol. **1**:297, 1941. Frazer, R., and Smith, P. H.: Simmonds' Disease or Panhypopituitarism (Anterior): Its Clinical Diagnosis by the Combined Use of Two Objective Tests, Quart. J. Med. **10**:297, 1941.

attempting to analyze and interpret the results of various tests in the light of present knowledge regarding the roles of various hormones in the regulation of carbohydrate metabolism. Thus, as these authors indicated, one of the hormones of the adrenal cortex accelerates the breakdown of tissue proteins, and the liberated amino acids are converted, in part, by the liver to dextrose and glycogen; the glycogen stores in the body are thus increased, which facilitates recovery from the hypoglycemic state. The glycotropic hormone of the pituitary, on the other hand, inhibits the action of insulin in lowering the blood sugar, although it does not raise the dextrose level of the blood.[15]

In January 1942 Meduna, Gerty and Urse [16] reported that the blood in certain cases of schizophrenia had an anti-insulin effect when tested in rabbits in a manner similar in principle to that of de Wesselow and Griffiths. However, instead of using standardized rabbits, they drew their conclusions from comparing the effect of the injection of blood of normal persons and epileptic patients with that of the injection of blood of schizophrenic patients. Meduna and his co-workers injected 1 unit of insulin subcutaneously in rabbits weighing 2 Kg. one hour after the injection of 20 cc. of blood intraperitoneally. The blood sugar of each rabbit was determined before the injection of insulin and again thirty minutes after injection and hourly thereafter for five hours.

The anti-insulin effect observed in the blood of 60 per cent of the schizophrenic patients was manifest by a decrease in the drop in the blood sugar of the rabbits on injection of insulin and a more rapid return of the blood sugar to the original levels, as compared with the effect of the blood of normal and of epileptic persons.

If increased amounts of an anti-insulin factor are present in the blood of certain schizophrenic patients, one might expect to find a decreased insulin sensitivity when tested by the method of Csépai and Ernst.

MATERIAL AND METHODS

In this paper are reported the results of such tests carried out on a group of 16 patients with mental disorders. In 7 patients the possible presence of an anti-insulin factor in the blood was tested according to a modified method of de Wesselow and Griffiths.[13] On 3 patients both tests were performed. In all, 20 patients were studied. All but 3 of the patients had schizophrenia and subsequently were given a course of insulin shock therapy. The results of the tests will also be compared with the doses of insulin which were required to produce coma in these patients. One of the patients had a depression and presented

15. Young, F. G.: Glycogen and the Metabolism of Carbohydrate, Lancet **2**:297, 1936. Footnote 14.

16. Meduna, L. J.; Gerty, F. J., and Urse, V. G.: Biochemical Disturbances in Mental Disorders: I. Anti-Insulin Effect of Blood in Cases of Schizophrenia, Arch. Neurol. & Psychiat. **47**:38 (Jan.) 1942.

clinical manifestations of Parkinson's disease together with features of the Cushing, or hyperadrenocortical, syndrome. The case of this patient has been reported in detail, with postmortem studies, by Schlesinger and Horwitz.[17]

All of the patients received the regular hospital diet, which was liberal in its carbohydrate content.

Insulin Sensitivity Tests.—The tests were performed with the patients in the postabsorptive state, approximately sixteen hours after the last meal. A test dose of 0.06 unit of insulin per kilogram of body weight was injected intravenously. The blood sugar level was determined on capillary blood from the finger tip before and one-half, one and two hours after the injection. The Folin-Wu method was employed, and yeast fermentation was used to determine the "true," or fermentable, blood sugar.[18]

Test for Anti-Insulin Factor in Serum.—A group of rabbits were given 0.5 or 0.6 unit of insulin intravenously as a test dose eighteen hours after food had been removed from their cages. The blood sugar level was determined for each animal before and fifteen, thiry, forty-five and sixty minutes after the injection of insulin. Blood from the marginal vein was used for these determinations. This test was repeated once or twice at approximately weekly intervals in order to determine the "standard" response of each animal to its test dose of insulin. After a rest period of approximately one week, each rabbit received intravenously 10 cc. of the serum to be tested. Three hours thereafter blood was taken from the marginal vein for the determination of the blood sugar, and then the test dose of insulin used for standardization of the particular animal was injected intravenously and the blood sugar curve determined, as in the standardization tests previously described. This blood sugar curve was compared with the "standard" blood sugar curve in order to determine whether the injection of serum was associated with any anti-insulin effect. Of the several "standard" curves obtained for each rabbit, that one was chosen in which the initial postabsorptive blood sugar level most closely approximated the curve obtained during the serum test. Each rabbit was used only once for this test. The serum used in each test was separated from venous blood obtained one day prior to the test. The patients were in the postabsorptive state when the blood was obtained.

OBSERVATIONS AND RESULTS

Insulin Sensitivity Tests.—It will be observed in table 1 that 13 of the 16 patients tested had conditions diagnosed as various types of dementia praecox, 2 had psychoneuroses and 1 a neuroendocrine disturbance. The initial levels of blood sugar in the postabsorptive state, although variable, were within the normal range in all cases. Three of the patients with dementia praecox (cases 8, 9 and 10) and the patient with an neuroendocrine disorder (case 20) manifested insulin resistance,

17. Schlesinger, N. S., and Horwitz, W. A.: Neuropsychiatric Disorders Occurring in Cushing's Syndrome, Am. J. Psychiat. **96**:1213, 1940.

18. Folin, O., and Wu, H.: Simplified and Improved Method for the Determination of Sugar, J. Biol. Chem. **41**:367, 1920. Peters, J. P., and Van Slyke, D. D.: Determination of Fermentable Sugar in Blood by Measuring the Decrease in Reducing Substances Caused by Yeast Fermentation, in Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 478.

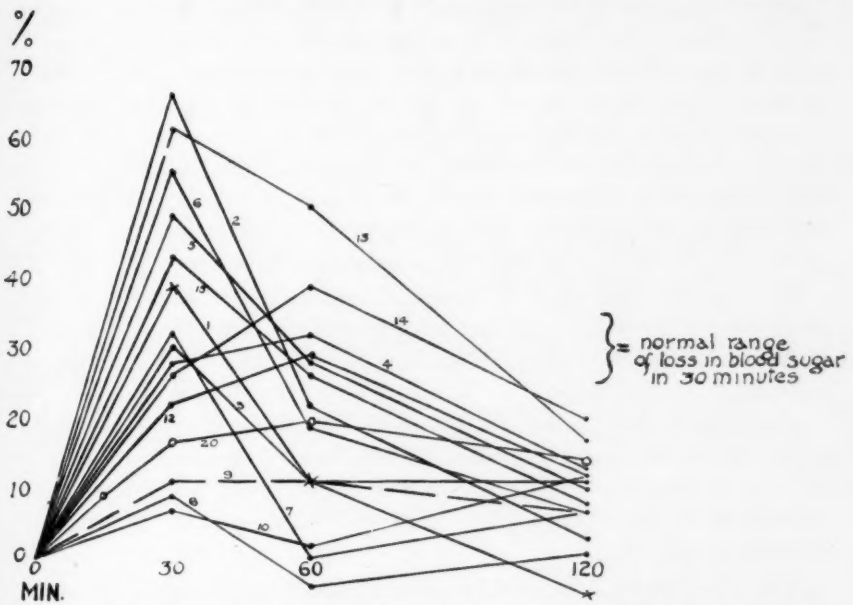
TABLE 1.—*Effect of Intravenous Injection of Insulin Test Dose on True Blood Sugar Level*

Patient	Case No.	Age, Yr.	Sex	Weight, Kg.	Insulin Test Dose, Units	Loss in Blood Sugar in Percentage of Initial Level *				Diagnosis †	Coma Dose of Insulin, Units	Comment
						Before	After ½ Hour	After 1 Hour	After 2 Hours			
L. S.	1	37	M	53.6	3.6	0 (82)	39 (50)	11 (73)	—5 (86)	P. N.	110	
G. T.	2	35	M	74.5	4.9	0 (88)	66 (30)	23 (69)	3 (85)	D. P. U. (I)	75	
F. S.	3	19	F	71	4.7	0 (106)	31 (73)	11 (94)	11 (94)	D. P. C. (I)	140	
					4.7	0 (112)	38 (69)	23 (86)	17 (92)	.....	...	Test after 17 insulin shock treatments
B. B.	4	27	M	70	4.6	0 (87)	28 (63)	32 (59)	13 (76)	D. P. U. (U)	250	
S. S.	5	37	M	78	5.2	0 (80)	49 (41)	28 (58)	10 (72)	P. N.	...	Patient left hospital without treatment
I. J.	6	29	M	66	4.4	0 (96)	55 (43)	19 (78)	7 (89)	D. P. H. (I)	85	
H. W.	7	26	M	78	5.2	0 (85)	32 (58)	0 (86)	7 (79)	D. P. S. (U)	385	Anti-insulin effect + with serum test (see table 2)
G. S.	8	16	M	55	3.8	0 (76)	9 (69)	—3 (78)	1 (75)	D. P. H. (U)	80	
				59	4.0	0 (97)	57 (42)	28 (69)	9 (88)	.....	...	Test after 20 insulin shock treatments
C. R.	9	16	M	53.6	3.6	0 (100)	11 (89)	11 (89)	7 (93)	D. P. C. (U)	60	
S. M.	10	24	M	70.5	4.7	0 (102)	7 (95)	2 (100)	12 (90)	D. P. H. (U)	90	Anti-insulin effect ++ with serum test (table 2)
B. K.	11	24	F	56.3	3.8	0 Specimen lost	.. (36)	.. (73)	.. (87)	D. P. H. (M. I.)	60	Patient much improved after insulin shock treatment but had relapse
M. E.	12	36	F	55.5	3.7	0 (104)	22 (81)	29 (74)	12 (92)	D. P. C. (R)	260	Anti-insulin effect + with serum test (table 2)
				56.5	3.8	0 (81)	41 (48)	27 (59)	7 (75)			Insulin sensitivity test repeated after 1 mo. of insulin shock treatment
S. S.	13	32	F	59	3.9	0 (107)	62 (41)	50 (54)	17 (89)	D. P. P. (I)	50	Patient improved after insulin shock treatment, but relapse followed
D. F.	14	17	F	69	4.6	0 (98)	27 (72)	39 (60)	20 (78)	D. P. H. (I)	90	Patient improved after insulin shock treatment, but relapse followed
J. Q.	15	33	F	51.8	3.5	0 (98)	43 (56)	26 (73)	8 (90)	D. P. P. (I)	60	Patient improved after insulin shock treatment, but relapse occurred
L. G.	20	28	F	60	4.0	0 (114)	9 (95)	19 (92)	14 (98)	N. E.	...	Patient had clinical manifestations of Parkinson and Cushing syndromes

* Figures in parentheses indicate true blood sugar levels, expressed in milligrams per hundred cubic centimeters of blood.
† D. P. C. indicates dementia praecox, catatonic type; D. P. H., hebephrenic type; D. P. P., paranoid type; D. P. S., simple type; D. P. U., undetermined type; N. E., neuroendocrine disturbance, and P. N., psychoneurosis.
I, means improvement; M. I., great improvement; R, recovery, and U, no improvement after insulin shock treatment.

as shown by the small drop in blood sugar one-half hour after the intravenous administration of the test dose of insulin. In 4 of the patients (cases 4, 12, 14 and 20) there was some evidence of insulin resistance in that the blood sugar did not drop to the lowest level until one hour after the administration of insulin. Frazer, Albright and Smith [14] expressed the opinion that such delay is indicative of insulin resistance.

It will also be noted that all except the insulin-resistant patients (cases 8, 9, 10 and 20) had a loss in blood sugar equal to 25 per cent or more of the initial level. In cases 3, 6 and 13 the loss in blood sugar



Loss of blood sugar expressed in percentages of the initial level, due to intravenous injection of a test dose of insulin.

one-half hour after insulin was over 50 per cent of the initial blood sugar level (graph). This is a marked fall in blood sugar, since Csépai and Ernst stated that a drop of 25 to 35 per cent in thirty minutes is normal and Frazer, Albright and Smith,[14] using 0.1 instead of 0.06 unit of insulin per kilogram of body weight injected intravenously in normal subjects, reported a drop in blood sugar of 50 per cent.

Three of the patients (cases 3, 8 and 12) tested again after receiving insulin shock treatment showed a greater drop in blood sugar after such therapy. This appears to be contrary to the observation of Banting and his co-workers [19] that insulin shock treatment in a case of schizophrenia

19. Banting, F. G.; Franks, W. R., and Gairns, S.: Anti-Insulin Activity of Serum of Insulin-Treated Patient, Am. J. Psychiat. **95**:562, 1938.

Figures in parentheses indicate true blood sugar levels, expressed in milligrams per hundred cubic centimeters of blood.
D. P. C., indicates dementia praecox, catatonic type; D. P. H., hebephrenic type; D. P. P., paranoid type; D. P. S., simple type; D. P. U., undetermined type;
N. P., manic-depressive psychosis, manic type; M. D., manic-depressive psychosis, depressive type.
I., means improvement; M. I., great improvement; R., recovery, and U., no improvement after insulin shock treatment.

with pronounced insulin resistance resulted in an increase in insulin resistance. In fact, patient 8, who originally showed resistance to insulin, exhibited pronounced insulin sensitivity (table 1) after insulin shock treatment.

As regards recovery from the lowered blood sugar level, it will be noted that in 8 patients the blood sugar level two hours after the injection of insulin was still 10 to 20 per cent below the initial postabsorptive blood sugar level (table 1 and graph).

Tests for Anti-Insulin Action of Serum.—The serums of 7 patients with various types of dementia praecox were tested for their anti-insulin effect on standardized rabbits. The test was repeated on H. W. (case 7) after he had received forty-three insulin shock treatments. The injection of serum from patients H. W. and S. M. (cases 7 and 10; table 2) was associated with an appreciable antagonistic effect on the action of the test dose of insulin. This was particularly evident in case 10. The antagonistic effect was manifested both in the lesser degree to which the blood sugar fell and in the more rapid return of the blood sugar of the test rabbits to their respective initial postabsorptive levels.

The serum of patient H. W. (case 7), when retested after the patient had received forty-three insulin shock treatments, showed almost complete disappearance of its previous antagonistic effect on the action of insulin.

In patients M. E. and S. W. (cases 12 and 18) the antagonism to the action of insulin associated with the injection of serum was manifest only by a more rapid recovery to the initial blood sugar level. In patients R. K., N. M. and J. G. (cases 16, 17 and 19) no antagonistic action was observed.

Glen and Eaton,[4b] in an interesting study of a diabetic patient who was exceedingly resistant to insulin, found that her serum had a pronounced antagonistic effect on the action of insulin in test rabbits. They also found, on retesting these rabbits with insulin alone forty-eight hours or more after the "serum test," that the antagonistic effect was even more pronounced. As an explanation of this observation the investigators suggested that the injection of the serum had stimulated an increased production of antagonistic substances in the test animals. In view of these claims, 5 of the rabbits were retested with insulin alone one week after they had been used for the regular "serum tests" because of the possibility that any effect antagonistic to the action of insulin resulting from the injection of serum might become more manifest at this time. By comparing the effects of the test dose of insulin at this time with the effects obtained in the standardization tests, it will be seen from table 2 that in cases 7, 16 and 18 indications of insulin resistance were

TABLE 2.—*Effect of Injection of Serum of Patients on Insulin Sensitivity of Rabbits*

TABLE 2.—*Effect of Injection of Serum of Patients on Insulin Sensitivity of Rabbits*

Patient	Case No.	Sex	Age	Time of Insulin Injection, Min.	Insulin Sensitivity of Rabbits: Standardization Test (A) Blood Sugar, Mg. per 100 Cc.	Standardization Test (A) Percentage Loss *	Three Hours After Serum (B) Blood Sugar, Mg. per 100 Cc.	Three Hours After Serum (B) Percentage Loss *	One Week After Serum Test (C) Blood Sugar, Mg. per 100 Cc.	One Week After Serum Test (C) Percentage Loss *	Result of Test B	Coma Dose of Insulin, Units	Comment
R. K.	16	F	33	0	111	0	97	0	104	0			Weight of rabbit 2.7 Kg.; test dose of insulin 0.6 unit. Diagnosis, D. P. P.†; patient much improved, after shock therapy
				15	73	34	63	35	74	29			
				30	68	39	62	36	82	21	—	80	
				45	87	22	74	24	89	14			
				60	100	10	79	19	93	11			
S. M.	10	M	24	0	134	0	131	0	Not tested		++	90	Weight of rabbit 1.7 Kg.; test dose of insulin 0.5 unit. Diagnosis, D. P. H.; patient unimproved after insulin shock treatment
				15	115	14	132	0					
				30	75	44	93	29					
				45	Specimen lost	..	128	2					
				60	87	35	123	8					
M. E.	12	F	36	0	121	0	104	0	110	0			Weight of rabbit 2.7 Kg.; test dose of insulin 0.6 unit. Diagnosis, D. P. C.; patient recovered but only long after treatment was completed
				15	116	4	85	18	82	25			
				30	99	18	92	11	84	24	+	260	
				45	94	22	97	5	98	11			
				60	105	13	104	0	103	6			
N. M.	17	M	22	0	108	0	121	0	115	0			Weight of rabbit 2.5 Kg.; test dose of insulin 0.6 unit. Diagnosis, D. P. C.; patient remained unimproved after shock therapy
				15	82	24	69	43	85	26		Over	
				30	76	30	73	40	80	30	—	200	
				45	90	17	87	28	93	19			
				60	90	17	93	23	103	10			
S. W.	18	M	16	0	118	0	113	0	109	0			Weight of rabbit 2.5 Kg.; test dose of insulin 0.6 unit. Diagnosis, D. P. H.; patient unimproved after shock therapy
				15	108	8	101	11	89	18			
				30	88	25	88	22	103	5	+	125	
				45	88	25	106	6	106	3			
				60	103	14	115	0	109	0			
J. G.	19	M	26	0	128	0	130	0	Not tested		—	140	Weight of rabbit 1.8 Kg.; test dose of insulin 0.5 unit. Diagnosis, D. P. H.; condition improved after shock therapy
				15	101	10	101	22					
				30	84	34	60	54					
				45	85	34	87	33					
				60	91	29	103	21					
H. W.	7	M	26	0	123	0	110	0	126	0			Weight of rabbit 1.8 Kg.; test dose of insulin 0.5 unit. For diagnosis and condition see table 1
				15	102	11	86	13	85	33			
				30	60	51	64	42	62	51	++	385	
				45	67	46	91	17	90	29			
				60	85	31	101	8	97	23			
					132	0	121	0	Not tested		..	...	Test performed on a new rabbit after patient had received 43 insulin shock treatments; blood taken 7 days after last treatment. Weight of rabbit 1.3 Kg.; test dose of insulin 0.5 unit
					115	13	73	40					
					82	38	75	38					
					94	29	90	26					
					90	24	98	19					

* Loss of blood sugar is expressed in percentages of the initial blood sugar level.
† See footnote to table 1.

obtained. This resistance was somewhat more pronounced than in the previous "serum tests" in cases 16 and 18, but less so in case 7.

Combined Tests.—On patients H. W., S. M. and M. E. (cases 7, 10 and 12) both tests were performed. S. M., whose serum gave the strongest antagonistic effect to insulin, (table 2) was also most resistant to the intravenous test dose of insulin (table 1).

Relation of Tests to Coma Dose of Insulin.—It might be expected that patients who were more resistant to the insulin test dose or whose serum was more antagonistic to the action of insulin would require larger doses of insulin to produce coma. However, a comparison of the results obtained with the tests and the subsequent coma dose required by each patient showed no strict correlation (tables 1 and 2).

COMMENT

It was pointed out earlier in the paper that many factors enter into the regulation of carbohydrate metabolism. Any increase in insulin resistance that might result from a low carbohydrate intake can be ruled out for the patients studied, since all were eating a regular hospital diet with a high carbohydrate content.

Meduna and his co-workers claimed that the blood of 60 per cent of the schizophrenic patients which they tested had an antagonistic effect on the action of insulin. They injected 20 cc. of blood into a rabbit weighing 2 Kg. in each test, an amount equivalent to 500 cc. for a 50 Kg. person. However, a person weighing 50 Kg. would have a blood volume of about 4 to 5 liters, or the equivalent of about ten times the amount of blood per kilogram of body weight injected into the test rabbits. On the basis of such calculation, it might be expected that if any substance antagonistic to the action of insulin was present in increased amounts in the blood of schizophrenic patients, it would be detected by studying the effect of the injection of small test doses of insulin on the blood sugar level of such patients. Since a group of normal persons was not tested, the normal standard response as given by Csépai and Ernst (Fernbach [11a]), whose test was employed, was used as the basis for comparison. According to this test, the intravenous injection in a normal person of 0.06 unit of insulin per kilogram of body weight should produce a drop in the level of the blood sugar of 25 to 35 per cent in one-half hour, with a return to the original level in one to two hours. It may perhaps be of significance that in only 2 of the patients (cases 1 and 8; table 1 and graph) did the level of the blood sugar return to the original fasting level in two hours. In 7 of 12 of the patients with schizophrenia the final blood sugar two hours after insulin was 10 per cent or more below the original fasting level. In only

4 of the patients (cases 8, 9, 10 and 12; table 1 and graph) was the blood sugar level depressed less than 25 per cent one-half hour after the injection of the test dose of insulin. It would appear, therefore, that the factors antagonistic to the lowering of the blood sugar by insulin differ at least in part from those factors which bring about recovery from the hypoglycemic state. This is in keeping with the results of many recent investigations [20] and the point made by Frazer and his co-workers [14] in their recent publications, that the two effects, namely, lowering of the blood sugar and recovery from the hypoglycemic state, should be considered separately. Only 4, or 33 per cent, of the patients with dementia praecox showed interference with the former effect in their insulin sensitivity tests, as compared with the 60 per cent in the series of Meduna and his co-workers, in which the blood was tested in rabbits, as previously described. The factors responsible for the difference in the results obtained with the two tests will require further investigation.

In the tests on the effect of the patient's serum on the response of the rabbit to insulin, (tests made according to a procedure similar to that of de Wesselow and Griffiths [13]), 3 of the 6 patients showed varying degrees of antagonism to the blood sugar–lowering effect of insulin. Although the number of patients studied is small, the results approach the 60 per cent obtained by Meduna. The injection of serum of 4 of the patients was accompanied by an increased rate of recovery of the lowered blood sugar toward the initial fasting level. Here, again, as in the insulin sensitivity tests, the effects on the lowering of the blood sugar and on recovery were not identical.

It was pointed out previously that the insulin sensitivity tests bore no strict relation to the dose of insulin required to produce coma during the subsequent insulin shock treatment. This may indicate some independent condition in the central nervous system which renders it more or less susceptible to the hypoglycemic state. This would be in keeping with the observation that the central nervous system of different persons varies in susceptibility to noxious agents.

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It may also be of interest to indicate that in both the tests employed some of the patients showed increased sensitivity to insulin (tables 1 and 2 and graph). In this connection, it may be pointed out that Himsworth [6a] expressed the opinion, on the basis of his studies, that blood contained some substance which was necessary for the activation of insulin and that insulin resistance was due to an inadequate amount of this activating substance. This view, however, would not account for those cases in which the injection of serum or blood has an antagonistic effect on the action of insulin in the experimental animal. It is possible that the amount of substances in the blood which increase or decrease the activity of insulin may vary with different persons.

It has been pointed out by various investigators that dementia praecox is probably not a clinical entity and that the pathogenesis is not the same in all cases. It is surprising, therefore, that Meduna and his co-workers found that all of the patients, namely, 60 per cent of the total number studied, who were considered to have typical schizophrenia had an increased amount of anti-insulin factor in their blood, whereas those patients in whom no such increase in anti-insulin factor was found were said to present atypical clinical features. In the clinical material classified as schizophrenia which has been investigated thus far, no peculiar clinical features were apparent which differentiated the cases so as to account for the differences obtained in the tests. The effect of insulin shock therapy on the clinical course did not appear to bear any strict relation to the degree of insulin sensitivity or to the presence of anti-insulin factor in the serum. A decrease in insulin resistance following a course of insulin shock treatments was not necessarily accompanied by a change in the clinical condition. This tends to throw doubt on the importance of anti-insulin mechanisms in the pathogenesis of schizophrenia. However, the number of patients studied was insufficient to determine whether or not any significant statistical correlation exists. This will require more extensive investigation.

SUMMARY AND CONCLUSIONS

A group of 16 patients, consisting of 13 with dementia praecox, 2 with psychoneurosis and 1 with a neuroendocrine disturbance, were tested as regards their sensitivity to test doses of insulin as reflected by the changes in the blood sugar level, according to the method of Csépai and Ernst.

Of the patients with dementia praecox, some showed a normal response and others either an increased or a decreased sensitivity to the test dose of insulin.

A group of 7 patients with dementia praecox were studied by a method similar to that of de Wesselow and Griffiths with regard to the

possible presence of substances in the serum which affect the action of insulin.

The serum of some of the patients showed a pronounced antagonistic effect on the action of insulin, while others showed little or no effect.

The results obtained with both tests were compared with the report of Meduna and his co-workers, in which it was claimed that increased amounts of substances antagonistic to the action of insulin were present in the blood of schizophrenic patients.

The possible role of insulin antagonism in the pathogenesis of dementia praecox is discussed and the need for further investigations indicated.

A patient with depression associated with a combined Parkinson and Cushing syndrome showed evidence of resistance to the blood sugar–lowering effect of insulin, associated with slow recovery to the initial blood sugar level. The latter effect is in keeping with the claim of Fernbach that patients with Parkinson's disease show slow recovery from the depressed blood sugar level.

The delayed recovery from the lowered blood sugar level observed in the patients with dementia praecox may indicate a disturbance in the physiology of the neurovegetative system.

No strict correlation was found between the tests and the subsequent dose of insulin required to produce coma during insulin shock. The significance of this observation is discussed.

722 West One Hundred Sixty-Eighth Street.

EFFECTS OF DESTRUCTION OF HYPOTHALAMUS BY TUMOR

VINCENT P. COLLINS, M.D.
BOSTON

This paper is a report of the clinical and pathologic sequelae of a slowly growing tumor involving the floor and walls of the third ventricle in such a manner as to destroy all nuclei of the hypothalamus and to sever functionally the hypophysial stalk, while not disturbing adjacent regions or obstructing the flow of cerebrospinal fluid. The progress of the patient's illness and the observations at autopsy are given in detail because they emphasize a number of aspects of the complicated relationship of the hypothalamus to the pituitary gland and the other endocrine glands. Some observations offer clinical support for results of animal experimentation in this field. The significance of other findings, some of which are of obscure importance, must be left to the judgment of the reader in whose field they lie.

REPORT OF A CASE

History.—N. N., an unmarried woman aged 28, was admitted to the New England Deaconess Hospital, under the care of the Lahey Clinic. Semicomatose on admission, she died within thirty-two hours, on Nov. 14, 1940.

She was born at full term, on Dec. 29, 1911, and weighed 12 pounds (5,443 Gm.) at birth. In early infancy there was a six week period in which she was subject to violent crying spells; during these spells she would become cyanotic and then suddenly pass into a quiet sleep. She did not begin to talk or walk as soon as the other children in her family, and even as she grew older she was apt to stumble and fall when running. She started to school at the age of 5 and was considered of average intelligence. She was a nervous, restless child, given to crying spells and tantrums, but alert and fun loving. Childhood illnesses included measles, without complications, frequent colds and gastrointestinal upsets with vomiting. During this period she was underweight, but during her eleventh summer she began to gain weight, with an increase of 10 pounds (4.5 Kg.) in two months.

The onset of the menses occurred at 12 years of age. The periods were regular and lasted four to five days, and the flow was "profuse." She entered high school at the age of 14, showed some musical talent, played the violin and sang well. At 16 years of age she weighed about 120 pounds (54.4 Kg.).

When she was 17, she suffered a ruptured appendix, which required drainage. It was during hospitalization that excessive thirst was first noted by her family. This continued for the next ten years, and during this time she would arise two to three times a night and pass large amounts of watery urine. A strong psychic

From the Laboratory of Pathology, New England Deaconess Hospital.

factor was present, for the sight of a roadside spring while motoring produced an irresistible craving for water. No records of fluid intake and output were known to have been made. It was only shortly after the appendectomy that her menses began to decrease in amount of flow, although they still occurred at regular intervals. Somewhat later hot flashes developed, which were described by her family as resembling those occurring during the menopause. During this period, and from time to time later in life, her family noted a yellow tinge to her eyes and skin. A change in personality was observed. Whereas she had previously been lively and full of fun, she now became quiet and reserved.

In her twentieth year she entered a nursing school. During this period "nervousness" and crying spells were pronounced. This condition was ascribed in part to concern over her menstrual disturbances and fear that she would not be normal. After six months in training, repair of a hernia at the site of her previous operation was necessary. She did not complete her training, but remained at home for the next two years. During this time her menses ceased completely and did not recur. She began to complain of the cold for the first time. This sensitivity became marked, and at times her fingers were blue with cold when other members of the family were not uncomfortable. During the next few years she held several positions as nursemaid, housekeeper or practical nurse. Her nervousness continued to be manifested by crying spells; children "got on her nerves," and she feared to be alone or to handle dying patients. Her thirst and diuresis continued, as did her gain in weight, which had now reached about 150 pounds (68 Kg.).

At the age of 26 she sought medical attention because of the increasing weight, sensitivity to cold and mild lethargy. A basal metabolic rate was determined to be — 19 per cent, in July 1938, and a diagnosis of hypothyroidism (myxedema) was made. She was given thyroid, 1 grain (0.065 Gm.) daily, the dose being increased to 3 grains (0.195 Gm.) daily. With this treatment her basal metabolic rate rose to — 16 per cent in September 1938 and to + 2 per cent in November 1938. At this time the blood sugar was reported to be 120 mg. per hundred cubic centimeters, and she was told she had mild diabetes, for which she was placed on a diet. The basal metabolic rate fell to — 11 per cent in January, 1939. She was said to have felt better, although there was no appreciable loss of weight. No change in thirst or diuresis was noted, for the significance of these was not appreciated.

From this time she was subject to frequent "colds" which elicited mild respiratory symptoms, but were accompanied by elevations of temperature to 103 F. Observations by her sister revealed a daily elevation to 99 to 100 F. and a pulse rate of about 100 a minute.

During her twenty-eighth year mental and emotional changes appeared. She was suddenly discharged from a position as housekeeper for some reason not divulged by her employer, but in some way related to her change in personality and habits.

Lethargy was a prominent feature, and when at home she slept a great deal of the day. She might fall asleep immediately after breakfast, or even in the middle of a conversation. In February 1940 she held a bookkeeping position for two weeks, during which she appears to have handled the accounts well, but her memory was failing notably. She would forget the day or the time. For a while she herself was aware of something being wrong and said, "It will be a terrible tragedy if I don't get well soon." Her family found numerous notes written to remind herself of things to be done. She began to behave oddly, talked in a silly fashion and counted her church funds over and over. On several

occasions, in abrupt temper tantrums she struck her mother and sister. For some time she had been careless about the taking of thyroid, and in April 1940 the basal metabolic rate was determined to be —36 per cent. She now ceased taking thyroid altogether, and the polydipsia and polyuria, which had somewhat diminished, disappeared entirely during the last six months of her life.

In June 1940 she was hospitalized for five weeks and a diagnosis of encephalitis was made. She was treated with sulfonamide drugs and vomited a good deal. During the summer months following her return home she reached her maximum weight of 160 pounds (72.6 Kg.). Her appetite, which had been good, became ravenous. Mental deterioration was progressive. Conversation was limited to remote happenings and childish comments on her immediate environment, although she had occasional brief lucid intervals. She was frequently disoriented and expressed a pitiful wish "to go home." She might leave the house and be helplessly lost a short distance away. If restrained, she would fly into a sudden rage. She would sometimes arise in the morning and prepare to leave for some position she had previously held. As time went on the object of this preparation receded to earlier positions and finally to school or Sunday school. In October 1940 she began to be subject to periods of confusion, lasting ten to fifteen minutes and occurring two to three times daily. During these attacks she was disoriented, did not recognize her family and talked volubly but irrelevantly. During this time there was increasing weakness. When she sat down, her knees would collapse under her and she would fall into the chair. Her neck seemed unable to support her head, which dropped forward on her chest. Her family noted muscular twitchings in her arms. She walked with a stumbling gait and tripped over things, but never actually fell. During sleep periodic breathing was observed, with an abrupt interval of apnea. Although stuporous periods were increasingly long, one week before death she played the piano and sang for a visitor, and during the motor trip to the hospital she aroused occasionally and recognized landmarks along the way. She was admitted to the New England Deaconess Hospital on Nov. 12, 1940.

Physical Examination.—On admission the patient was in a stuporous condition, from which she could be roused to only fair cooperation. She was obese; her complexion was pale and her skin smooth and dry, but not thickened. There was some puffiness about the eyes, but no peripheral edema. The eyebrows were thin in the outer third; the body hair was scant; the hair of the scalp thin but not coarse. The blood pressure was 90 systolic and 60 diastolic, the temperature 99 F., the pulse rate 120 and the respiratory rate 20. The heart beat was rapid, with regular rhythm. Examination of the chest, abdomen and extremities revealed essentially a normal condition.

Neurologic Examination.—The pupils were irregular, the right being larger than the left, and reacted well. No ocular palsy was noted. The fundi showed engorged vessels; the disks were reddened and a little hazy, but the optic cups were present. The neck was slightly rigid. The arms were moved a little; the legs, not at all. There were occasional twitching movements of the arms. Reflexes in the arms were hyperactive and equal on the two sides. There was cogwheel rigidity of both arms. A Hoffmann sign was present bilaterally. The abdominal reflexes, the knee jerks and the left ankle jerk were absent. The plantar reflex was normal. There was no response to pinprick over the body or the extremities. On lumbar puncture clear fluid was obtained, under a pressure of 150 mm. of water. A roentgenogram of the skull revealed no abnormality.

Course.—A diagnosis of craniopharyngioma was considered. In the hospital she received intravenous injections of 5 per cent dextrose and high carbohydrate nourishment by Levine tube. Twelve hours after admission her temperature rose and the pulse and respiratory rates began to mount, and clinical signs of bronchopneumonia developed. She sank into a deeper coma from which she could not be roused. She was given sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and placed in an oxygen tent, but her condition became steadily worse and she died on her second day in the hospital, thirty-two hours after admission.

Laboratory Data.—Examination of the cerebrospinal fluid showed no red blood cells, 2 white cells per cubic millimeter, 41 mg. of sugar, 970 mg. of chlorides (sodium chloride), 78 mg. of total protein and a slight trace of globulin. The colloidal gold curve was normal. The Wassermann reaction was negative.

Urinalysis showed specific gravities of 1.019 and 1.021, a trace of albumin, 1.2 to 0.6 Gm. of sugar per hundred cubic centimeters, 11 to 12 red blood cells and 18 to 20 white blood cells.

The red cell count was 3,390,000, the hemoglobin concentration 65 per cent and the white cell count 5,250, with 37 per cent polymorphonuclear leukocytes, 53 per cent lymphocytes and 10 per cent large mononuclear leukocytes. The nonprotein nitrogen of the blood measured 50 mg. and the sugar 0.14 mg. per hundred cubic centimeters; the carbon dioxide-combining power of the blood was 60 volumes per cent; the serum protein 6.0 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.27, the blood chlorides (sodium chloride) 774 mg. and the blood cholesterol 191 mg. per hundred cubic centimeters.

Gross Autopsy Observations (ten hours post mortem).—The body was 64 inches (160 cm.) in length and weighed an estimated 140 pounds (63.5 Kg.). There were fulness about the face, especially in the infraorbital regions, and moderately well developed infraclavicular fat pads. The hair of the scalp was dark brown and silky; the eyebrows were sparse, especially in the lateral half, and the axillary and pubic hair was absent. The breasts were small and the nipples poorly developed. The mons veneris was not well formed. The labia minora and the clitoris were vestigial. The extremities were well formed and relatively slender. There was no pitting edema. The panniculus adiposus was 5 cm. in thickness over the abdomen. The serous cavities were normal.

Brain: The brain weighed 1,240 Gm. A mass arising from the hypothalamic region presented in the cisterna interpeduncularis as a rounded, encapsulated, yellow, cystic swelling, about 2 cm. in diameter. The diaphragma sellae was slightly flattened, but the sella turcica was not distorted and the pituitary was not compressed. The mass extended from the cerebral peduncles posteriorly to the lamina terminalis anteriorly. Laterally there was no invasion of the paraolfactory area, the uncus or the hippocampal gyrus. The optic chiasm was not invaded or grossly distorted, although the mass extended superior and anterior to it. The hypophysial stalk protruded from the cystic mass in its usual position. The corpora mamillaria could not be identified. On section, a multiloculated cystic mass was observed to have replaced the floor of the third ventricle. This cyst measured 2.5 cm. in its anteroposterior dimension and extended 0.8 cm. to either side of the midline. The third ventricle and the foramens of Monro were not obstructed. Multiple sections of the cerebral hemispheres, the cerebellum and the brain stem revealed no further pathologic change.

Pituitary: The gland weighed 620 mg. and was not remarkable grossly. There was no distortion or compression.

Other Organs: The heart weighed 230 Gm.; the lungs weighed 340 Gm. each and were not remarkable. The spleen weighed 240 Gm. Its pulp was dark, with visible malpighian corpuscles. The pancreas showed moderate fatty infiltration. The gastrointestinal tract was essentially normal throughout. The liver weighed 1,300 Gm. Its capsule was smooth and the border somewhat rounded. On section, the parenchyma was oily and tan in color, and bulged slightly beyond the capsule. The adrenal glands weighed 3.5 Gm. each. The cortex was only lightly pigmented. The kidneys each weighed 100 Gm. and, together with the ureters and bladder, were not remarkable. The uterus and cervix measured over all 5 by 3 by 2 cm. The lining endometrium was pale, smooth and thin. The ovaries each measured 2 by 1 by 0.5 cm. The capsules were thickened, wrinkled

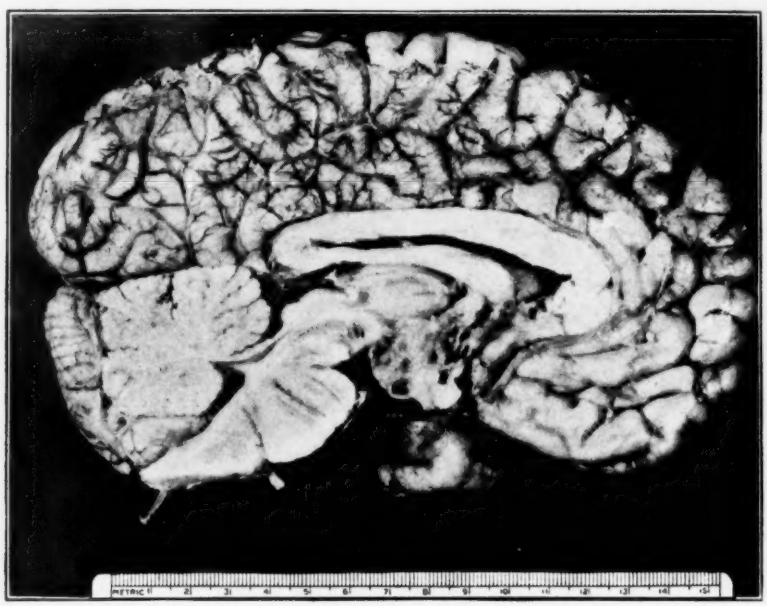

Fig. 1.—Brain, showing destructive lesion of the hypothalamus.

and pale gray. On section the substance was pink gray, with no macroscopic cysts. The thyroid weighed 14.5 Gm. Its capsule was smooth and firm. On section the exposed surface was pale pink gray. There was an increase in fibrous tissue, with no visible colloid. The thymus weighed 6.5 Gm.

Microscopic Examination.—Hypothalamus: The tissue was fixed in dilute solution of formaldehyde U. S. P. Sagittal sections were made of the right side and coronal sections of the left. Paraffin sections were stained with hematoxylin and eosin, phosphotungstic acid hematoxylin and Nissl's technic.

The floor and walls of the third ventricle were replaced by a degenerating tumor. The type cell was large, with copious, pale cytoplasm and fibrillary processes. It had a large, oval, pale nucleus with scanty chromatin material concentrated at the periphery and one or two eccentric nucleoli. Rare mitotic figures were encountered. Many cells were undergoing degeneration and showed vacuolation and loss of cytoplasmic and nuclear detail. The distribution of the process suggested

that it had originated in the floor of the third ventricle and spread upward in the lateral walls. Careful study of multiple sections of this region failed to identify any persistent nuclei of the hypothalamus. The supraoptic nuclei in particular were sought but not located. The disappearance of these nuclei may have been due to destruction of axons in the supraopticohypophysial tract, to direct invasion or to

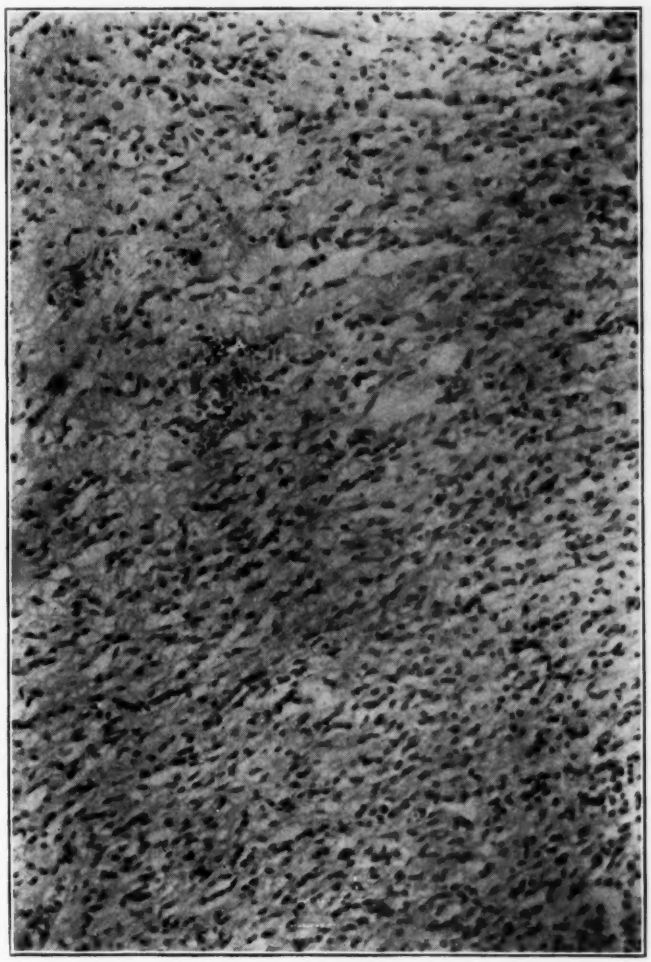

Fig. 2.—Posterior lobe of the pituitary, showing cellular condensation. × 150.

indirect pressure or to a combination of these factors. Yet, while the hypothalamus was completely destroyed, there was no invasion of the brain stem, thalamus or adjacent structures.

Pituitary: Material fixed in solution of formaldehyde U. S. P. was stained with hematoxylin and eosin, phosphotungstic acid hematoxylin and iron alum hematoxylin and phloxine and by Mallory's azan method and Bodian's silver technic.

Sections of the anterior lobe were normal in appearance; granular eosinophils and basophils were present in at least roughly normal proportions, although detailed cell counts were not made. The blood supply appeared adequate. In the posterior lobe, however, there was increased cellularity. The cells were apparently glial, and nothing resembling pituicytes was encountered. Bodian's silver preparation revealed no nerve fibers in the stalk. Here, too, the blood supply was good, and numerous capillaries filled with red cells were observed.

Heart, Lungs and Gastrointestinal Tract.—Sections of these organs were essentially normal.

Liver: Orientation of liver cords between the portal areas and the central vein areas was lost, owing to a conspicious degree of fatty vacuolation of the liver cells, the latter varying in type from large signet ring forms to foam cells. Moderate nuclear vacuolation was noted. Scattered individual cells were undergoing degeneration and were surrounded or invaded by polymorphonuclear leukocytes. There was well marked retention of bile pigment, both intracellular and within bile canaliculi. Fibrous tissue was not appreciably increased. The portal vein areas were not remarkable except for slight lymphocytic infiltration. The central vein areas were not engorged.

Adrenal: The cortex was very thin, due to a decrease in the size of individual cells of the three zones. In the zona glomerulosa the nests of cells were separated by an increased amount of loose connective tissue stroma. The cytoplasm was pale and granular and in many instances was undergoing disintegration. There were, however, a few remaining islands of plump cells with foamy cytoplasm. The nuclei were large and round. Some had a moderate amount of granular chromatin material, but in many the nucleoplasm was a homogeneous orange brown. Cords of the zona fasciculata were short, but for the most part straight and clearcut. The cells were small, had dark eosinophilic and finely granular cytoplasm and were almost completely devoid of vacuoles. The nuclei were dark and sharply outlined, and many lacked apparent chromatin material and had an orange tint. Owing to the diminished cell size, the nuclei appeared closely packed. The nuclei of the zona reticularis were entirely devoid of vacuoles but otherwise resembled those of the zona fasciculata. The medulla was ill defined. The cells were diminished in number; they were diffusely scattered through loose connective tissue, with engorged capillaries. The cytoplasm had a distinct orange tint, and the nuclei were oval or round, with scanty, granular chromatin material.

Kidney: The glomeruli were large. The tuft filled the capsule and appeared to contain an increased number of nuclei, but there was no appreciable increase in cement substance and capillaries of the tuft were thin walled and filled with red blood cells. The juxtaglomerular bodies were unusually large and prominent. Many tubules were filled with granular debris, and the lining epithelium was completely disintegrated, but these might be adjacent to well preserved tubules.

Uterus: The myometrium was normal, although individual smooth muscle fibers were very small. The endometrial glands were scanty and were lined by columnar epithelium. The nuclei were dark and occupied the greater part of the cell. The cytoplasm was eosinophilic, with no trace of vacuolation. Some superficial glands had undergone cystic dilatation. An occasional gland extended deep into the myometrium. Cells of the endometrial stroma were closely packed with small, dark, spindle-shaped nuclei, resembling those of fibroblasts. The capillary bed was scanty. There was light lymphocytic infiltration beneath the cervical epithelium, and the cervical glands were scanty.

Tube: The infoldings of the lining mucosa were coarse and fibrotic. Lining epithelial cells were dark and crowded together.

Ovary: The germinal epithelium of the surface of the ovary was represented only by the rare, flattened, pavement type of cells. The cortex contained numerous primordial follicles and several graafian follicles, but no corpora lutea. There were several large corpora albicantia. The stroma was cellular, but the cells for the most part were slender and spindle shaped. There was a rich capillary

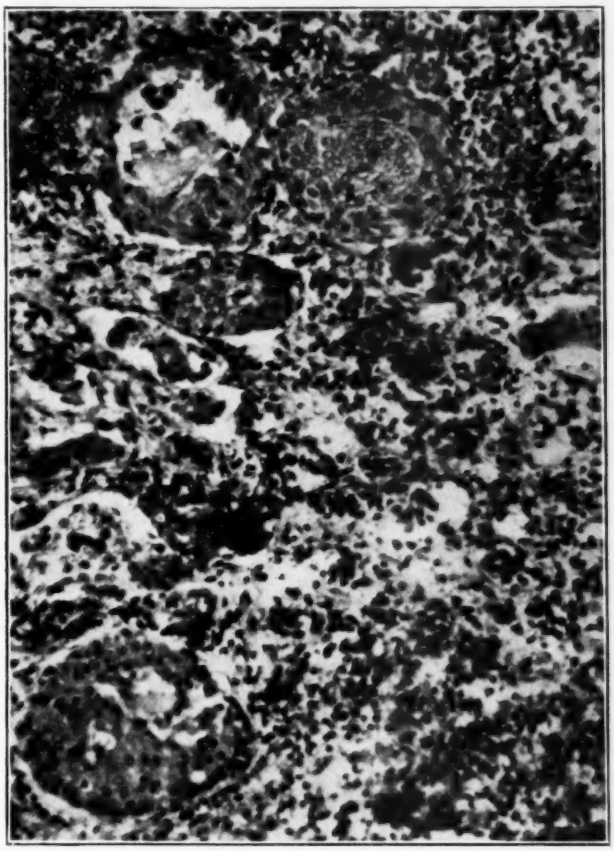

Fig. 3.—Thyroid, showing conspicuous lymphocytic infiltration, epithelial metaplasia and masking of normal architecture. × 225.

bed, particularly in the deeper portions of the ovary. The arteries showed well marked medial thickening.

Aorta: The intimal thickening was pronounced, owing to a myxomatous ground substance containing widely separated, plump fibroblasts and a few vacuolated phagocytes, with scattering of polymorphonuclear leukocytes. Muscle fibers in the media were separated by homogeneous, neutral-staining material up to three or four times the thickness of muscle cells.

Thyroid: Throughout the gland there was diffuse increase in fibrous stroma, as well as diffuse lymphocytic infiltration with focal concentration, but no well formed germinal centers. Numerous plasma cells and rare polymorphonuclear leukocytes were encountered. The follicles were not reduced in number, but were indistinct because of distortion and decrease in size. Most of the follicles were lined by low cuboidal epithelium with widely spaced nuclei and had a small central lumen with only a trace of pale colloid. In many no lumen was present and the follicle was represented by a clump of eight to ten plump epithelial cells. Some of the cells were large and formed eccentric heaps or even completely filled the lumen; in some instances these cells had borders suggestive of epithelial bridges. Occasional follicles were lined by flattened epithelium and distended with darkly staining colloid. There were numerous small foci of plump, eosinophilic Hürthle cells. Arterioles and small arteries showed distinct thickening of the media. There was a fair capillary network throughout the gland.

Skin: The epithelium showed slight excess cornification. Hair follicles were scarce and atrophic, although the erector pili muscles appeared normal. Sebaceous glands were few, and for the most part the cells were inactive. The corium was thick. Cellular elements were scanty. Collagen fibers were coarse and distorted in orientation.

Thymus: The fatty tissue of the thymus gland contained numerous foci of lymphoid tissue, with Hassall's corpuscles.

COMMENT

The clinical course of the polydipsia and polyuria and the lesions observed at autopsy in this case confirm in many details the known anatomic relationship between the hypothalamus and the posterior lobe of the pituitary and the present concept of the physiology of diabetes insipidus.

The hypophysial stalk in man contains an estimated 100,000 nerve fibers, derived almost wholly from the supraoptic nuclei.[1] These are distributed chiefly to the infundibular process, and in the rabbit and rat some are seen to terminate as pericellular nets enclosing single parenchymal cells.[2] Section of the stalk results in nearly total disappearance of cells of the supraoptic nuclei. The median eminence, the infundibular stem and the pars nervosa undergo characteristic atrophy, with hypercellularity due to close-packed, oval or elongated nuclei. No pituicytes can be identified.[3]

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2. Brooks, G. M., and Gersh, I.: Innervation of the Hypophysis of the Rabbit and Rat, Endocrinology **28**:1, 1941.

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This unit is intimately bound up with water metabolism and the causation of diabetes insipidus. Fisher, Ingram and Ranson [4] summed up knowledge of this condition thus:

> Diabetes insipidus is essentially an hypophyseal deficiency syndrome caused by a diminution or total absence of the antidiuretic hormone of the neural lobe of the hypophysis when the latter is extirpated or becomes atrophic secondary to interruption of the supra-optic-hypophyseal tracts.

In man, rat and cat complete removal or destruction of the anterior lobe prevents polyuria on removal or injury of the neurohypophysis. In the dog the increased water exchange is reduced but not abolished.[5]

Thyroidectomy abolishes diabetes insipidus in the dog [6] and reduces polyuria in the cat. In the hypophysectomized diabetic dog, polyuria is resumed on administration of anterior pituitary extract or thyroid powder.[7] Moreover, administration of thyroid intensifies the diabetes in dogs and induces excessive diuresis in normal dogs.[8] Blotner and Cutler [9] demonstrated the relief of diabetes insipidus in human beings following thyroidectomy and the reestablishment of polydipsia and polyuria with the administration of thyroid.

If the history in the present case is interpreted in the light of the autopsy observations, it may be presumed that the development of the diabetes insipidus paralleled the destruction of the supraoptic nuclei and infundibulum, with resultant atrophy of the neurohypophysis. When a diagnosis of hypothyroidism was made and thyroid medication was instituted, the polyuria was prolonged, if not intensified. The disappearance of the diabetes insipidus as thyroid was discontinued is in keeping with the effect of thyroidectomy in abolishing the polyuria, for histologic examination of the thyroid gland in this case demonstrated complete loss of function, in fact, functional thyroidectomy.

Two reports of the results of operative section of the hypophysial stalk further confirm the experimental observations. In the course of

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4. Fisher, C.; Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and Neurohumoral Control of Water Balance, Ann. Arbor, Mich., Edwards Brothers, Inc., 1938.

5. Gersh, I.: Water Metabolism: Endocrine Factor, A. Research Nerv. & Ment. Dis., Proc. **20**:436, 1940.

6. Mahoney, W., and Sheehan, D.: Pituitary-Hypothalamic Mechanism: Experimental Occlusion of the Pituitary Stalk, Brain **59**:61, 1936.

7. Keller, A. D.: Hypophyseal-Thyrotropic Mechanism Essential for Occurrence of Diabetes Insipidus in Its Maximal Form, Proc. Soc. Exper. Biol. & Med. **36**:787, 1937.

8. Biggart, J. H., and Alexander, G. L.: Experimental Diabetes Insipidus, J. Path. & Bact. **48**:405, 1939.

9. Blotner, H., and Cutler, E. C.: Total Thyroidectomy in the Treatment of Diabetes Insipidus, J. A. M. A. **116**:2739 (June 21) 1941.

an exploratory craniotomy, Dandy [10] divided the pituitary stalk without damage to contiguous parts of the hypothalamus or the pituitary. After operation permanent diabetes insipidus developed. At the time of publication, eleven years later, the patient had undergone two normal pregnancies and showed no endocrine disturbance other than diabetes insipidus. Rasmussen and Gardner [1] reported a case of operative section of the stalk in a 46 year old man with severe hypertension. At the same time it was necessary to cauterize the superior surface of the anterior lobe to control hemorrhage. After operation the hypertension improved, but diabetes insipidus did not develop and no endocrinologic evidence of disturbed function of the anterior lobe of the pituitary was noted. At the time of death, five months later, examination of the pituitary revealed cellular condensation and atrophy of the posterior lobe, no appreciable change in the pars intermedia and fibrosis and reduction of the anterior lobe to about two-fifths the average amount. The last change was ascribed to cauterization at the time of operation. A loss of 85 per cent of the cells of the supraoptic nuclei was observed and interpreted as resulting from section of the processes in the hypophysial stalk. The failure of diabetes insipidus to develop may be due to two factors: persistence of a portion of the hypothalamicohypophysial system in the tuber cinereum or partial destruction of the anterior lobe of the pituitary.

The anatomic evidence for nervous control of the function of the anterior lobe is on a less sound basis. Sympathetic fibers derived from the carotid plexus were early demonstrated to penetrate the anterior lobe in contact with the sheaths of minute blood vessels,[11] but it is thought that these fibers are vasomotor rather than secretory.[12] Brooks and Gersh [2] demonstrated that some of the nerve fibers descending in the hypophysial stalk enter the pars intermedia and reach the pars anterior by passing around the residual lumen of Rathke's pouch. These observations have been taken to indicate a neural control of the function of the anterior lobe mediated by the hypophysial stalk. In the stalk-sectioned rabbit, ovulation, which normally follows the stimulation of coitus, does not occur.[13] This phenomenon does not result in spontaneously ovulating animals, such as the rat and guinea pig. In these

10. Dandy, W. E.: Section of Human Hypophyseal Stalk, J. A. M. A. **114**: 312 (Jan. 27) 1940.

11. Dandy, W. E.: Nerve Supply and Pituitary Body, Am. J. Anat. **15**:333, 1913.

12. Rasmussen, A. T.: Innervation of Hypophysis, Endocrinology **23**:263, 1938.

13. Brooks, C. M.: A Study of the Mechanism Whereby Coitus Excites the Ovulation-Producing Activity of the Rabbit's Pituitary, Am. J. Physiol. **121**: 157, 1938.

animals, however, exposure to cold normally stimulates the production of thyrotropic hormone and depresses that of gonadotropic hormone. After section of the stalk, this response does not occur.[14] Results of electrical stimulation of the central nervous system have suggested release of gonadotropic hormone by the anterior lobe.[15]

The efforts of numerous investigators have failed to demonstrate that the cervical sympathetic fibers and the carotid plexus play any part in governing the thyrotropic and gonadotropic functions of the anterior lobe.[12] The elaboration of hormone-like substances by neurons of the hypothalamus [16] and their passage through the portal system of veins accompanying the stalk to the anterior lobe have only recently begun to receive serious consideration, with the demonstration of the release of a luteinizing hormone from the anterior lobe by an acetylcholine-like substance from the hypothalamic region.[17]

If the results of experiments on laboratory animals may be applied to human beings, one might hypothesize the following relationships concerned with some of the interesting features of this case: The clinical and histologic evidence of depression of function of the ovaries, thyroid and adrenal glands might well be ascribed to a pathologic process primary in the anterior lobe of the pituitary. In fact, the disturbance closely resembles the picture of Simmonds' disease, described by Sheehan,[18] following the postpartum necrosis of the anterior lobe and characterized by general hypofunction of the endocrine glands, without cachexia. The histologic integrity of the anterior lobe of the pituitary, however, suggests its dependence for normal function on a higher center of control located in or acting through the area destroyed by tumor in this case. Destruction of this region has resulted in the failure of the apparently intact anterior lobe to produce gonadotropic, thyrotropic and adrenotropic factors. Further, the preservation of the anterior lobe with destruction of the hypothalamus suggests that if there are

14. Dempsey, E. W.: Relationship Between Central Nervous System and Reproduction Cycle in Female Guinea Pig, Am. J. Physiol. **126**:758, 1939. Dempsey, E. W., and Uotila, U. U.: Effect of Pituitary Stalk Section upon Reproductive Phenomena in Female Rat, Endocrinology **27**:573, 1940. Uotila, U. U.: Role of Pituitary Stalk in Regulation of Anterior Pituitary with Special Reference to Thyrotropic Hormone, ibid. **25**:605, 1939.

15. Marshall, F. H. A., and Verney, E. B.: The Occurrence of Ovulation and Pseudopregnancy in the Rabbit as a Result of Central Nervous Stimulation, J. Physiol. **86**:327, 1936.

16. Scharrer, E.: Neurosecretory Cells in Vertebrates, Anat. Rec. **70** (supp. 3): 101, 1938.

17. Taubenhaus, M., and Soskin, S.: Release of Luteinizing Hormone from the Anterior Hypophysis by an Acetylcholine-Like Substance from the Hypothalamic Region, Endocrinology **29**:958, 1941.

18. Sheehan, H. L.: Simmonds' Disease Due to Postpartum Necrosis of Anterior Pituitary, Quart. J. Med. **8**:277, 1939.

neural pathways, they are by no means as essential as is the neural connection of the pars nervosa, where section of the nerve pathways results in pronounced atrophic changes in the cellular elements. If the control is by a humeral mechanism, the cessation of production of such factors in the hypothalamus results in cessation of function of the anterior lobe, but in maintenance of its structure if the circulation through the portal system of veins is intact.

Although a diagnosis of diabetes mellitus had been made in this case a year and a half before the patient's death, the only available evidence is the single blood sugar determination of 120 mg. per hundred cubic centimeters and the presence in the urine of 1.2 Gm. of sugar per hundred cubic centimeters one hour after the intravenous administration of 450 cc. of a 10 per cent solution of dextrose. When there is evidence of diminished function of the anterior and posterior lobes of the pituitary, the adrenals and the thyroid, the secretions of all these glands being antagonistic to insulin, an increased sugar tolerance and a tendency to hypoglycemia would, rather, be expected. In fact, the short periods of mental confusion in the last few weeks of the patient's life could be interpreted as episodes of hypoglycemia.

The association of adiposity with lesions of the floor of the third ventricle is well known and bulimia is a frequent symtom in persons with tumor in this region. The girl's appetite was described as ravenous by her family, and her increasing adiposity paralleled the development of the hypothalamic lesion, particularly in the late stages. The overloading of fat within the liver is significant, but difficult to interpret. It is not a constant, or even a frequent, feature in the common type of obesity unassociated with organic lesion. It may be that direct control by neural or humeral mechanisms of storage and metabolism of liver fat is exercised by the hypothalamus normally, with secondary control of storage of fat in tissue depots. A simpler explanation lies in the chronic hypoglycemia before postulated, due to failure of normal insulin antagonists, with resultant morbid appetite and excessive intake of food.

Disturbances of sleep, such as the lethargy which was so prominent a feature in the last few months of the patient's illness, have been associated with pathologic processes in the region of the third ventricle since von Economo's work on encephalitis lethargica.[19] Cushing[20] described the gliomatous lesions involving the walls of the third ventricle as a form of brain tumor associated with hypersomnia.

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19. von Economo, L., and von Wagner Jauregg, J.: Baron Constantin von Economo: His Life and Work, translated by R. Spillman, New York, Ramsay Spillman, 1937.

20. Cushing, H.: Pituitary Body and Hypothalamus, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

The persistent low grade elevation of temperature, and possibly the occasional febrile episodes, with elevations to 103 F., may be interpreted as indicating a disturbance of the heat-regulating mechanism. The regulation of body temperature is effected in part by the hypothalamus through "physical temperature regulation," such as vasoconstriction, vasodilatation, panting or sweating, and in part by the anterior lobe of the hypophysis, which controls through the thyroid the "chemical temperature regulation." [21] Although the material in this case presents no new information on the location or function of the heat-regulating center in the hypothalamus, it demonstrates the persistence of mild hyperthermia even in the absence of the "chemical temperature regulation" ascribed to the thyroid. Raab [22] presented evidence that the thermoregulatory center was identical with the mechanism regulating normal absorption and oxidation of fat within the liver, which he took to be one of the essential factors in heat production.

A correlation of the personality changes with the areas or pathways destroyed is beyond the scope of this paper, but attention is called to the sudden episodes of temper tantrums and violence which occurred in the late stage of the patient's illness and to the resemblance they bear to rage reactions, or "sham rage," in decorticate animals. From his experiments Bard [23] concluded that the caudal portion of the hypothalamus, containing the posterior group of nuclei, was essential for the development of "sham rage," which, he stated, was the result of release of these primitive centers from cortical control. Keller,[24] however, demonstrated a rage response in a dog in which the descending hypothalamic fibers had been completely severed. He therefore concluded that a typical rage response is not dependent on an outflow of fibers from the hypothalamus and questioned whether the posterior hypothalamus is essential for a full blown rage reaction. The observations in this case would appear to support Keller's view.

SUMMARY

A case is reported which throws light on the function of the hypothalamus in man. The following abnormalities are ascribed to the destruction of the hypothalamus by tumor: diabetes insipidus; sup-

21. Hemingway, A.; Rasmussen, T.; Rasmussen, A. T., and Wikoff, H.: Effect of Cutting Pituitary Stalk on Physiological Temperature Regulation, Endocrinology **27**:212, 1940.

22. Raab, W.: Wärmeregulation und Fettstoffwechsel, Ztschr. f. d. ges. exper. Med. **53**:317, 1926.

23. Bard, P.: A Diencephalic Mechanism for the Expression of Rage, Am. J. Physiol. **84**:490, 1928.

24. Keller, A. D.: Rage Readily Excitable in a Dog with Descending Hypothalamic Fibers Severed, Am. J. Physiol. **129**:P396, 1940.

pression of function of the anterior lobe of the pituitary, the thyroid, the ovaries and the adrenal glands; disturbance of fat metabolism; disturbance of sleep; disturbance of thermal regulation, and disturbance of personality.

The role of the thyroid in diabetes insipidus is demonstrated, and information bearing on the anatomic and physiologic relationship between the hypothalamus and the anterior lobe of the pituitary gland is presented.

Dr. Edward W. Dempsey and Dr. Knox H. Finley, of Harvard Medical School, assisted in the examination of the pituitary and the hypothalamus.

630 West One Hundred Sixty-Eighth Street, New York.

SPINAL EPIDURAL GRANULOMA

REPORT OF A CASE

JAMES V. WARREN, M.D.
AND
JOHN ROMANO, M.D.
BOSTON

Recent observation on a patient who experienced spastic-ataxic paraplegia due to compression of the cord by an epidural granuloma led to consideration of the incidence, diagnosis and prognosis of this lesion. Because of the relative infrequency of the condition and the many diagnostic variables which existed in this instance, we present the following case.

REPORT OF CASE

C. H. W., a 45 year old, single, unemployed embalmer, was admitted to the Peter Bent Brigham Hospital for the second time on Aug. 1, 1940, complaining of inability to walk of two weeks' duration.

The family history was not pertinent.

Personal History.—The patient had been in excellent health until seven years before admission, when, at the age of 37, he sought medical advice because of dizziness and weakness. He was admitted to the Peter Bent Brigham Hospital for the first time on March 22, 1933, and examination showed evidence of hypertensive cardiovascular disease with minimal retinal changes, moderate enlargement of the heart and arterial pressures ranging from 180 systolic and 80 diastolic to 220 systolic and 100 diastolic. There was no evidence of cardiac decompensation. The Wassermann reaction of the blood was positive, although the Hinton reaction was negative. The spinal fluid at that time was clear and colorless and under an initial pressure of 170 mm. of water, with a prompt rise to 350 mm. and a rapid fall to 150 mm. following jugular compression and release. The fluid contained 1 lymphocyte per cubic millimeter; the serologic reaction was negative; the colloidal gold curve was normal, and the total protein content was 55 mg. per hundred cubic centimeters. During the following eighteen months the patient received inadequate antisyphilitic therapy, consisting of mercury, trivalent arsenicals and potassium iodide. The symptoms diminished in frequency and severity, and the patient was said to have been in relatively good health up to the onset of his present symptoms.

In the past the patient had drunk alcohol in moderate quantities, but during the past eighteen months he had consumed greater amounts. He often drank as much as 1 quart (950 cc.) of distilled liquor daily, and his food intake was diminished. With the exception of a "boil" on his nose, which he had two to three months before his second admission, he did not remember any extensive furunculosis or other source of infection. Three months before this admission he experienced a

From the Medical Clinic, the Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School.

syncopal episode of brief duration, and on recovery he found that his vision was blurred. Later he was able to see only with the left eye. One month later he had "red" urine for several days, with oliguria, nocturia, difficulty in starting the stream and swollen ankles. At this time he also complained of pain low in the back, which radiated along the iliac crests. Two weeks before admission he experienced numbness of the right great toe and leg, together with weakness. Later his left leg was involved, and as his disability increased, he was admitted to the hospital.

Physical Examination (August 1).—The patient appeared to be well developed and well nourished. He was unable to stand. The temperature was 99 F., the pulse rate 110, the respiratory rate 20 and the blood pressure 210 systolic and 100 diastolic. The significant physical findings were minimal sclerosis of the retinal vessels and moderate enlargement of the heart, with a slight basal systolic murmur.

Neurologic Examination.—The patient was aware and was not aphasic. There was left homonymous hemianopia. The cranial nerves were otherwise intact. The reflexes, strength, muscle volume and sensory modalities of the upper extremities were unaffected. The upper abdominal reflexes were active; the lower ones were absent, and there was upward excursion of the umbilicus when the patient sat up. The knee jerks were hyperactive, the right slightly more than the left, with unsustained clonus bilaterally. The ankle jerks were equal and hyperactive on the two sides, with sustained clonus on the right. The plantar responses were extensor. There was ataxia in the heel to knee and toe to object tests bilaterally. Vibratory sensation was impaired to the middorsal region, and position sense at the toes was affected. Both legs were weak and spastic, particularly the left. There were fine and coarse fibrillations of the left leg and buttock at rest, which increased on effort. Light touch, pinprick and ice were appreciated normally. The patient had difficulty in starting the urinary stream, and cystoscopic examination showed evidence of both acute and chronic cystitis, consistent with cord bladder.

Laboratory Studies.—The results of repeated urinalyses were without note except for the presence of many white blood cells in the sediment and repeated growths of Staphylococcus aureus on culture. Studies of the blood showed a minimal degree of secondary anemia and persistent leukocytosis, with a count of 12,000 to 16,000 cells per cubic millimeter and a normal differential count. Chemical determinations of the blood gave essentially normal results. The Hinton and Wassermann reactions of the blood were positive. Studies of the spinal fluid showed dynamic block, a high protein content, positive serologic reactions and no pleocytosis (table). Roentgenologic examination of the chest disclosed only moderate cardiac enlargement. Roentgenograms of the entire spine and intravenous pyelograms revealed no significant abnormality.

Course.—The oral temperature varied from 98 to 101 F., with commensurate pulse and respiratory rates. The arterial pressure remained elevated. The patient received antisyphilitic therapy, consisting of trivalent arsenicals, a bismuth compound and potassium iodide, for one month. His spastic-ataxic paraplegia progressed. During this interval investigations included pyelography, cystoscopy, roentgenography of the spine, chest and skull and repeated lumbar punctures. Iodized poppyseed oil was introduced in the lumbar subarachnoid space; the patient was tilted on the fluoroscopic table, and a myelogram was obtained, which indicated a funnel-shaped deformity and block opposite the twelfth thoracic vertebra.

Operation.—On September 16 a laminectomy was performed by Dr. Elliott C. Cutler, at the area noted in the myelogram. The muscles were friable and a

grayish pink, and a small drop of pus was expressed from them, culture of which revealed Staph. aureus. The laminas of the twelfth thoracic vertebra were cut with ease. A rather extensive extradural mass, extending well above the twelfth thoracic vertebra, was seen to compress the cord. A large fragment of the mass was excised. The pathologic diagnosis was that of a spinal epidural granuloma. Photomicrographs of the tissue may be seen in the illustrations.

On opening the dura below the mass, the cord seemed unaffected. A catheter could not be passed above the mass, at the level of the tenth or the eleventh thoracic vertebra. Further excision of the mass was not attempted because the initial surgical impression was that of a malignant neoplasm.

Data on the Spinal Fluid

Source	Lumbar	Lumbar	Lumbar	Lumbar	Lumbar Before Myelography with Iodized Poppyseed Oil
Date	3/22/33	8/3/40	8/4/40	8/29/40	9/11/40
Pressure, mm. H_2O					
Initial	170	180	110	130	....
On jugular compression	350	No change	Slow rise to 300 mm. after several trials	No change	....
On jugular release	150	No change	Slow fall to 260 mm.	No change	....
On abdominal compression	Not done	Rapid rise to 350 mm.	Rapid rise to 300 mm.	Rapid rise to 350 mm.	....
On abdominal release	Not done	Rapid fall	Rapid fall	Rapid fall	....
Amount of fluid removed, cc.	12	6	6	8	....
Final pressure, mm. H_2O	100	50	60	30	....
Color and transparency	Clear; colorless	Clear; yellow	Clear; faint yellow	Clear; faint yellow	....
White blood cells	1 lymphocyte	4 lymphocytes	—	1 lymphocyte	....
Red blood cells, no. per cu. mm.	0	240	4	2	....
Pandy reaction	+	++++	++++	++++	....
Total protein, mg. per 100 cc.	55	800	300	800	400
Colloidal gold reading	0000000000	0011123341	2344444411	5555555551	3443322111
Wassermann reaction	—	+	Unsatisfactory	+	—
Hinton reaction	Test not done	+	+	+	+
Comment	.....	No respiratory excursions	.....	.....	....

Postoperative Course.—The postoperative course was complicated by a persistent infection of the urinary tract and decubitus ulcer. Sulfanilamide therapy was given. There was no essential change in the patient's neurologic status at the time of discharge, on Dec. 17, 1940.

The patient returned to his home and was able to sit in a chair five to six hours a day. His appetite improved, and he gained 10 to 12 pounds (4.5 to 5.4 Kg.) in eight months. He returned to the outpatient clinic for irrigations of the bladder and antisyphilitic treatment. He was able to void spontaneously and had no remarkable difficulty with frequency, dribbling, burning or nocturia. He was unable to stand when he left the hospital, but in January 1941 (one month later) he began to stand and walk with support. In June 1941 he commenced to walk alone. He did not complain of numbness or tingling in his legs. One year after

operation physical examination revealed essentially the same condition as on admission. Neurologic examination revealed the same degree of hemianopia as before. He swayed slightly in the Romberg position and felt more at ease with his eyes open than closed. He was able to stand on each foot for a short period and to stand on tiptoe, but could not walk a straight line. The cranial nerves were

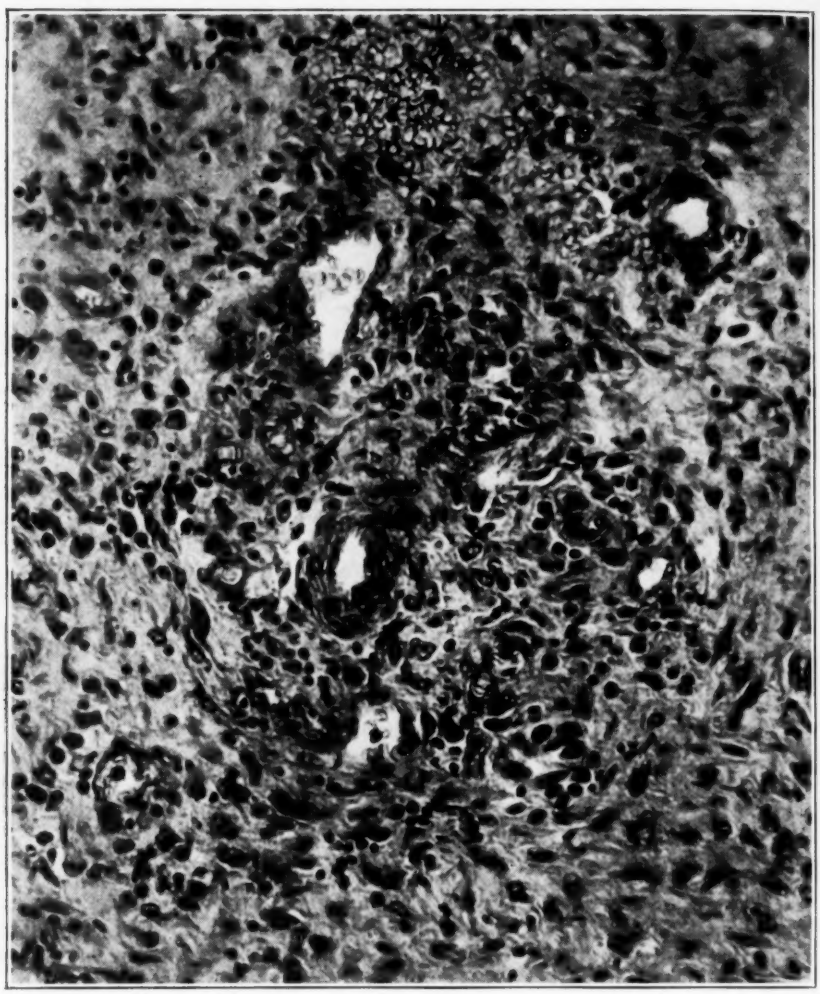

Fig. 1.—An average field in the region of involvement. The tissue consisted of newly formed capillaries and fibrous tissue infiltrated with lymphocytes and mononuclear cells. Polymorphonuclear leukocytes were more numerous in fields nearer the center of the lesion. Eosin and methylene blue; × 300.

intact. The neurologic status of the upper extremities was unaffected. The lower abdominal reflexes were still absent, and there was some residual weakness of the lower abdominal wall with upward excursion of the umbilicus. The cremasteric

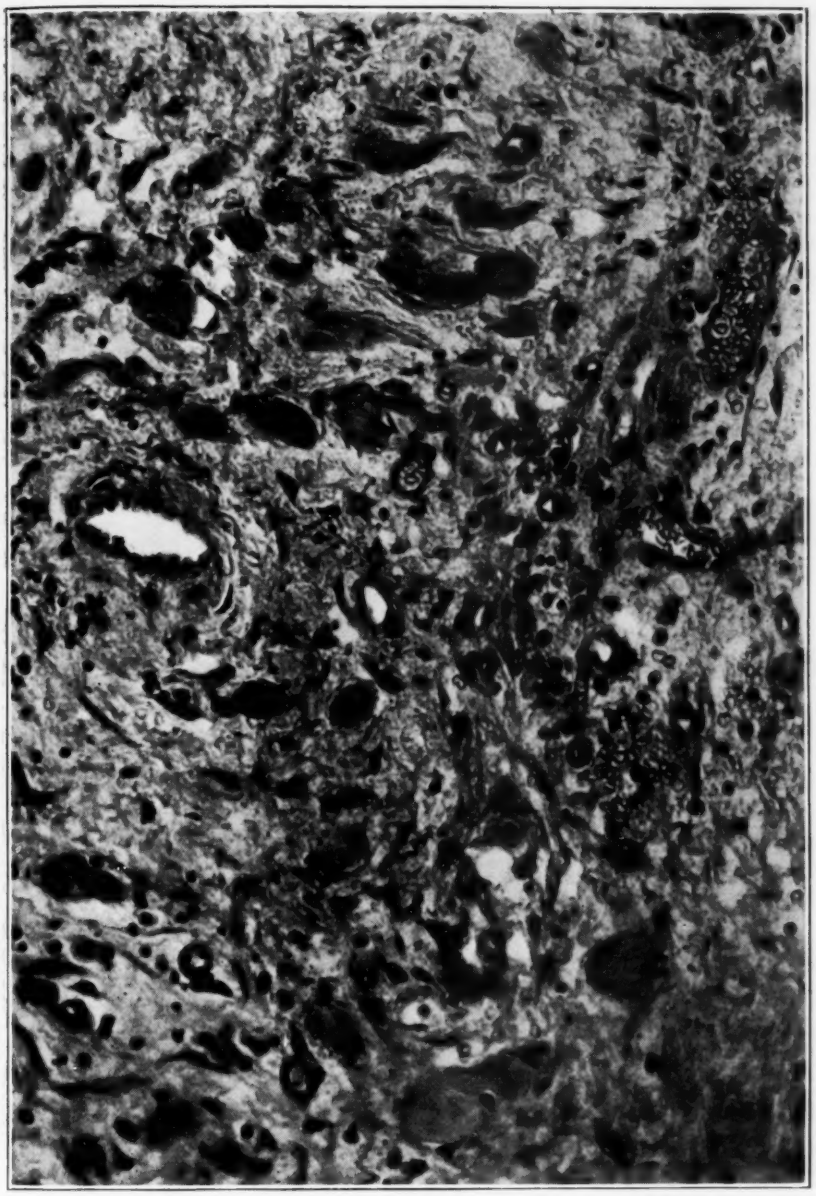

Fig. 2.—Extension of the granulomatous process into muscle. In a few preserved muscle fibers separated by fibrous tissue newly formed capillaries and lymphocytes were present. Eosin and methylene blue; × 300.

reflexes were equal and active on the two sides. The knee and ankle jerks, likewise, were equal and hyperactive on the two sides, with unsustained clonus. The weakest movement of the lower extremities was flexion. Heel to knee and toe to object tests were done well on both sides. In contrast to the results of previous examinations, position and vibratory senses were found to be intact. Light touch, pain

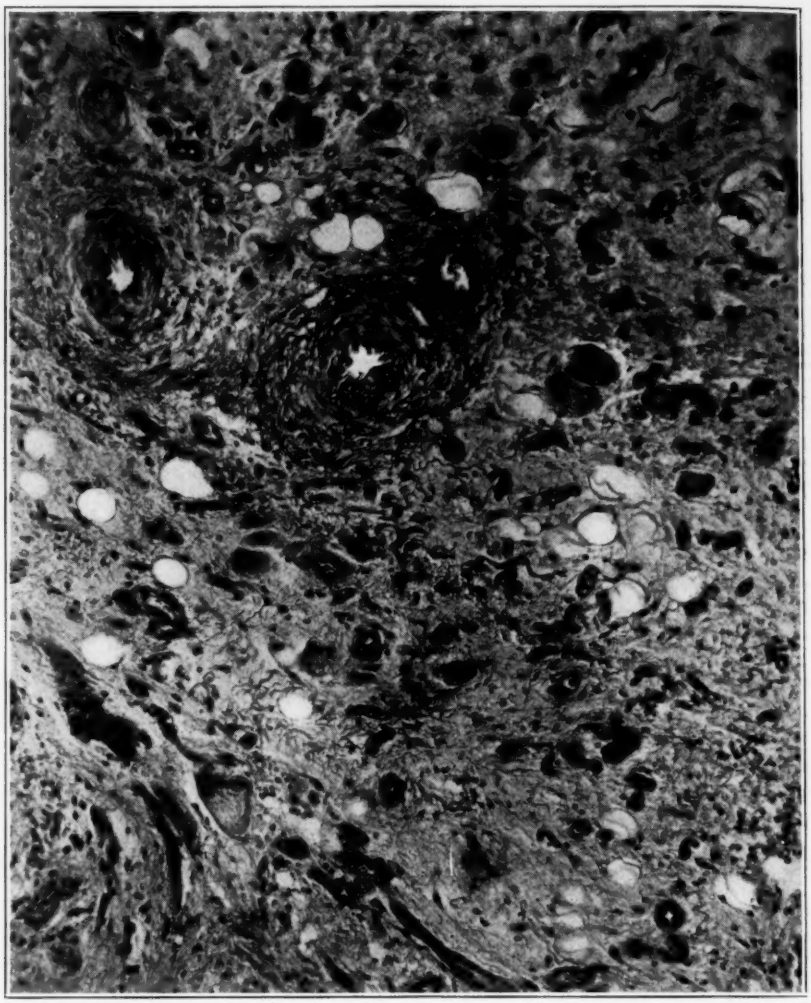

Fig. 3.—An area at the outer edge of the lesion. Scattered muscle fibers and fat cells were separated by small amounts of newly formed connective tissue, with scattered lymphocytes and mononuclear cells. Eosin and methylene blue; × 150.

and temperature senses were not involved. There was no remarkable loss in muscle volume. The operative wound was well healed, and there was no tenderness on percussion of the spine. Plantar responses were equivocal bilaterally, although most of the responses were flexor.

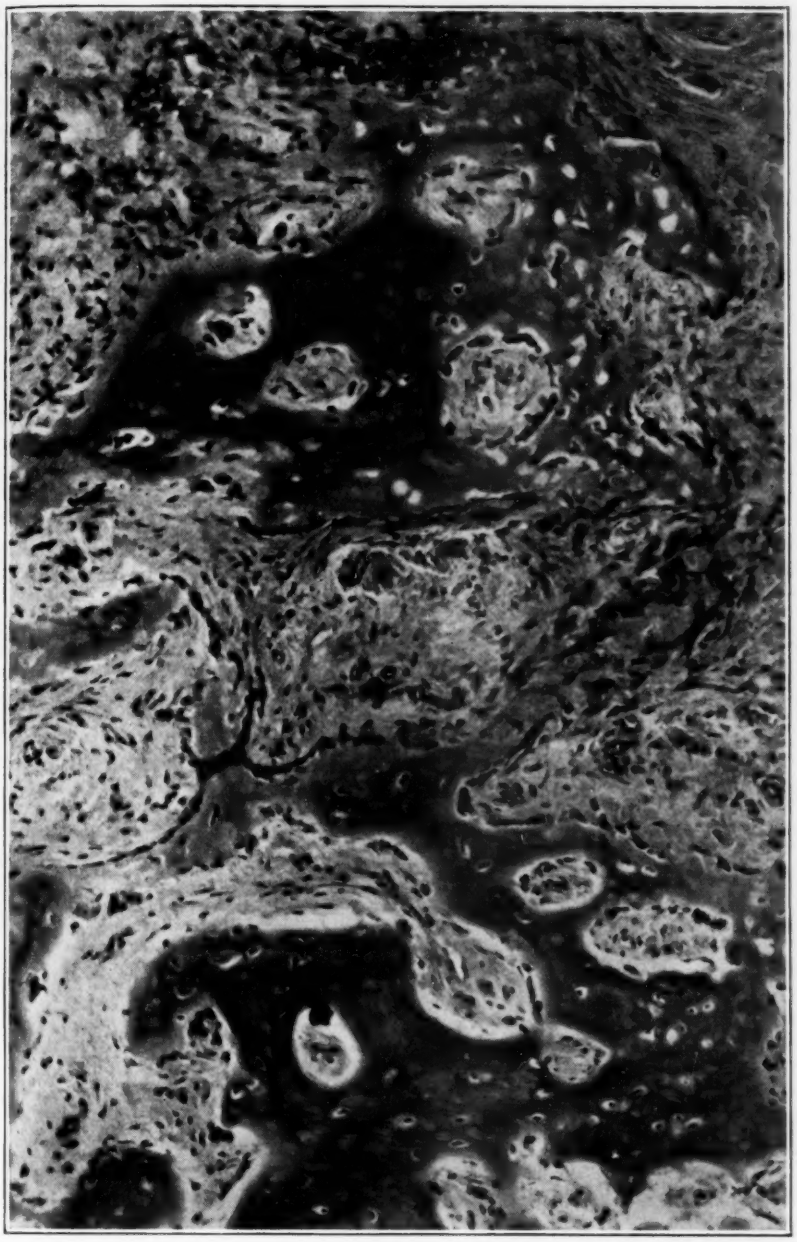

Fig. 4.—Region of new bone formation at the edge of a granulomatous area. This new bone had originated from the periosteum adjacent to the region of inflammatory involvement. Eosin and methylene blue; × 300.

This case presented considerable difficulty in diagnosis. With a history of syphilis, hypertensive cardiovascular disease, alcoholism and nutritional deficiency, together with an episode of syncope followed by left homonymous hemianopia, a number of etiologic factors were considered.

There was little doubt as to the neurologic findings. The patient had evidence of incomplete dynamic subarachnoid block, probably due to a space-occupying extramedullary lesion in the lower dorsal segments. In addition, he had left homonymous hemianopia. It seemed unlikely that the lesion could be attributed to changes in the cord following excessive ingestion of alcohol or nutritional deficiency, nor did it appear probable that vascular disease on a thrombotic basis would cause such a block. The diagnostic alternatives were such space-occupying lesions as (1) syphilitic gumma, (2) primary extramedullary neoplasm and (3) multiple or metastatic neoplastic foci. The evidences of syphilis included a positive serologic reaction of the blood in 1933, with subsequent inadequate treatment, and positive serologic reactions of the blood and spinal fluid at the time of the present examination. However, the serologic reaction of the spinal fluid in 1933 was negative, although the total protein content was 55 mg. per hundred cubic centimeters. It is known that the validity of the serologic response of the spinal fluid is questionable in those instances in which the serologic reaction of the blood is positive and the total protein content of the spinal fluid is greatly elevated.[1] In this case the Wassermann reaction of the spinal fluid was negative in the higher dilutions of the fluid. It seemed unlikely that the patient had neurosyphilis, as the spinal fluid gave a negative serologic reaction in 1933, which was probably some years after his initial infection. It was pointed out that if he did have a syphilitic space-occupying lesion, it could not be treated adequately with chemotherapy and surgical intervention was indicated. A second possibility was that of a primary extramedullary neoplasm at the lower dorsal segments. The history of root pain, the course of progressive compression and the evidence of subarachnoid block with elevation of the protein content and absence of cells made this diagnosis likely. Such a lesion did not explain the hemianopia, which was interpreted as an independent phenomenon, possibly due to cerebral thrombosis related to the hypertensive cardiovascular disease. The third possibility was that of multiple or metastatic neoplastic lesions arising from the kidney (the patient had an episode of "red" urine in the past), Hodgkin's disease or other neoplastic condition. This could account for the cerebral lesions as well as the changes in the cord. However, investigation of the blood, viscera and bones revealed no primary focus.

1. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, W. B. Saunders Company, 1938.

We did not consider an inflammatory process because of our unfamiliarity with chronic inflammatory epidural processes, because we had attributed the fever and leukocytosis to the cystitis, which was secondary to the neurogenic bladder and because there had not been evidence of cellular reaction in the spinal fluid. A "boil" that the patient had on his nose two or three months before the onset of the disability (mentioned in a student's note) had not been associated with his illness.

As stated previously, surgical intervention revealed a large extramedullary epidural mass, which on histologic section was observed to be an epidural granuloma. The sections consisted of granulation tissue, in which there was abundant evidence of acute and chronic inflammation. Most of the material was made up largely of rather cellular or more collagenous young connective tissue showing varying degrees of infiltration with plasma cells, eosinophils and lymphocytes. The lymphocytes and plasma cells predominated and at times formed such dense clumps that the fixed tissue elements were obscured. Occasional macrophages were seen. Polymorphonuclear leukocytes were scattered diffusely throughout the tissue, but in smaller numbers than were the lymphocytes. Rare dense collections of polymorphonuclear leukocytes, forming small abscesses, were encountered. Both the fixed tissue elements and the polymorphonuclear leukocytes showed varying degrees of necrosis. Occasional multinucleated giant cells were seen. In portions of the sections clumps and isolated gram-positive cocci were seen. The tissue was moderately vascular. In a few sections there was active bone formation, with osteoblasts. A distinct capsule could not be identified, and the lesion extended into neighboring striated muscle.

COMMENT

Dandy,[2] Watts and Mixter[3] and Browder and Meyers[4] have discussed thoroughly the etiology, symptomatology, treatment and prognosis of spinal epidural granuloma. Since the paper of Watts and Mixter, in 1931, in which they collected 6 cases from previous reports and presented 4 new ones, we have been able to find only 6 additional instances. A case not previously noted was reported by Ryerson[5] in 1922. Turnbull, Hyland and McKenzie[6] reported 1 case in 1933, and Browder and Meyers,[4] in 1937, and Cohen,[7] in 1938, each reporting 2 cases.

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2. Dandy, W. E.: Abscesses and Inflammatory Tumors in the Spinal Epidural Space, Arch. Surg. **13**:477 (Oct.) 1926.

3. Watts, J. W., and Mixter, W. J.: Spinal Epidural Granuloma, New England J. Med. **204**:1335, 1931.

4. Browder, J., and Meyers, R.: Infections of the Spinal Epidural Space: An Aspect of Vertebral Osteomyelitis, Am. J. Surg. **37**:4, 1937.

5. Ryerson, E. W.: Spastic Paraplegia Due to Infectious Granuloma on the Dura: Operation, Recovery, Arch. Neurol. & Psychiat. **7**:270 (Feb.) 1922.

6. Turnbull, F. A.; Hyland, H. H., and McKenzie, K. G.: A Staphylococcus Infection Producing an Inflammatory Mass Simulating a Spinal Cord Tumor, Canad. M. A. J. **28**:415, 1933.

7. Cohen, I.: Epidural Spinal Infections, J. Mt. Sinai Hosp. **5**:219, 1938.

The problem of spinal epidural infection may lie between the extremes of acute epidural abscess and chronic epidural granuloma. With few exceptions, the pyogenic organism associated with spinal epidural infections is the staphylococcus. Trauma and preceding purulent infection have played a provocative role in some instances. The pathologic process in the bone, the epidural space and the adjacent meninges and cord varies with the course and development of the epidural infection. The pathogenesis is thought to be by direct extension from an adjacent infection or by hematogenous or lymphogenous spread of the organism. The clinical symptoms vary with the site, size and age of the lesion. For the most part, there is a history of root pain followed by evidences of compression of the spinal cord. This and subarachnoid block, lymphocytosis of the spinal fluid, fever and leukocytosis are the essential features. Our patient had syphilis and other physical disease, with no lymphocytosis and questionably valid serologic evidence of syphilis presented by the spinal fluid.

SUMMARY AND CONCLUSIONS

The case of a patient with spastic-ataxic paraplegia due to compression of the cord by an epidural granuloma associated with Staph. aureus is presented.

The case presented considerable difficulty in diagnosis because of the coincidence of syphilis, hypertensive cardiovascular disease, alcoholism and nutritional deficiency. Absence of cells in the spinal fluid below the subarachnoid block was a further source of confusion.

Surgical removal and subsequent drainage of the granulomatous area led to considerable improvement.

Dr. Orville T. Bailey made the histologic studies and the photomicrographs of the tissue.

Emory University School of Medicine, Atlanta, Ga.
University of Cincinnati, Cincinnati.

EFFECT OF IODIZED POPPYSEED OIL ON THE SPINAL CORD AND MENINGES

AN EXPERIMENTAL STUDY

ROBERT L. CRAIG, M.D.
DURHAM, N. C.

Since the introduction of iodized poppyseed oil for myelography by Sicard in 1922 [1a] the increasing use of iodized oils intrathecally has occasioned much discussion as to the possibility of harmful effects on the meninges and the adjacent nerve tissue. It has been demonstrated that immediately after injection there is an acute cellular reaction, chiefly lymphocytic, usually associated with mild symptoms, such as slight rise in temperature, headache, pain and stiffness in the back and aggravation of root pains, reaching a peak within twelve to twenty-four hours and subsiding within four to seven days.[1] There is evidence that these acute meningeal reactions are due to iodic fatty acids and hydrogen iodide resulting from splitting of the iodized oil, either before or after injection, and that certain oils are more toxic than others.[2] Serious meningeal reactions have been reported in only 2 cases.[3] There have been occasional reports of chronic arachnoiditis discovered months or years after the injection of an iodized oil.[4] Several extensive surveys, however, have

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From the Neurologic Service of Duke Hospital and the Department of Internal Medicine, Duke University School of Medicine.

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2. Lindblom, A. F.: On the Effects of Various Iodized Oils on the Meninges, Acta med. Scandinav. **76**:395-402, 1931.

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4. (*a*) Maclaire, A. S.: Lipiodol in Neurosurgery, with a Report of a Case with Deleterious Results, Am. J. M. Sc. **170**:874-880, 1925. (*b*) Sharpe, W.,

(Footnotes continued on next page)

shown the rarity of any late harmful effects in patients reexamined two years or more after injection of the oil.[5] It has been found that after operation for ruptured intervertebral disk the residual iodized oil remains freely movable if the dura has not been opened but becomes rapidly encysted and immobile in cases in which the dura has been incised.[6] Complete reviews of the literature on the toxic effects of iodized oils will be found in recent papers by Walsh and Love,[4d] Brown and Carr [4e] and Garland.[5f] The current consensus, as expressed by Garland, is that fresh iodized poppyseed oil may be injected with safety into the subarachnoid space, the main drawback being that it remains visible indefinitely in roentgenograms. Garland expressed the belief that until a superior contrast medium is developed the use of iodized poppyseed oil is thoroughly justified in cases in which it is indicated, but that its indiscriminate use, without adequate preliminary study, is to be condemned.

In reviewing the literature on this subject, one finds that relatively little experimental work has been done to determine the exact effect of these oils on the tissues of the nervous system. It would, therefore, seem advisable to review in some detail the work which has been done and to reconsider the question of toxicity from an experimental point of view.

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and Peterson, C. A.: The Danger in the Use of Lipiodol in the Diagnosis of Obstructive Lesions in the Spinal Canal, Ann. Surg. **83**:32-41, 1926. (*c*) Bergerhoff, W.: Spätschädigung durch Iodipin, Fortschr. a. d. Geb. d. Röntgenstrahlen **36**:374, 1927. (*d*) Stölzner, H.: Ist die Myelographie mit Iodipin unbedenklich? Zentralbl. f. Chir. **54**:3274-3277, 1927. (*e*) Brown, H. A., and Carr, J. L.: The Effect of Lipiodol in the Subarachnoid Space, Surg., Gynec. & Obst. **68**:945-951, 1939.

5. (*a*) Globus, J. H., and Strauss, I.: Intraspinal Iodolography: Subarachnoid Injection of Iodized Oil as an Aid in Detection and Localization of Lesions Compressing the Spinal Cord, Arch. Neurol. & Psychiat. **21**:1331-1386 (June) 1929. (*b*) Globus, J. H.: Contribution Made by Roentgenographic Evidence After the Injection of Iodized Oil, ibid. **37**:1077-1082 (May) 1937. (*c*) Hampton, A. O., and Robinson, J. M.: The Roentgenographic Demonstration of Rupture of the Intervertebral Disk into the Spinal Canal After Injection of Lipiodol, Am. J. Roentgenol. **36**:782-803, 1936. (*d*) Selig, S., and Rubert, S. R.: The Effect of Large Amounts of Lipiodol Injected into the Spinal Subarachnoid Space, J. Mt. Sinai Hosp. **5**:363-368, 1938. (*e*) Garland, L. H., and Morrissey, E. J.: Intracranial Collections of Iodized Oil Following Lumbar Myelography, Surg., Gynec. & Obst. **70**:196-210, 1940. (*f*) Garland, L. H.: The Effect of Iodized Oil on the Meninges of the Spinal Cord and Brain, Radiology **35**:467-476, 1940.

6. Marcovich, A. W.; Walker, A. E., and Jessico, C. M.: The Immediate and Late Effects of the Intrathecal Injection of Iodized Oil, J. A. M. A. **116**: 2247-2254 (May 17) 1941.

In 1925 Peiper and Klose [7] reported a controlled series of experiments in which they gave rabbits intracisternal injections of 20 per cent iodized sesame oil, the amount of oil injected varying between 2 and 0.05 cc. In all the rabbits which received 2 cc. the ventricles and subarachnoid spaces were observed to be filled with saponified fat and the spinal cords were swollen and fissured, with large collections of oil in the gray and the white matter. This was also true of the control animals, which received 2 cc. of neutral sesame oil. This reaction, therefore, was attributed to mechanical pressure rather than to a toxic action. Similar, but less marked, pressure effects were found in rabbits which had received 1.5 and 1 cc. of the iodized oil. They found that 0.5 cc. was the maximum amount which could be tolerated by the rabbit without these mechanical effects. Animals receiving this amount showed inflammatory reactions in the meninges, necroses about the central canal and chromatolysis of some of the anterior horn cells. Marchi stains demonstrated degeneration of individual fibers in the posterior columns but no massive tract degeneration. Rabbits which had received 0.1 and 0.05 cc. of the iodized oil showed only inflammatory reactions in the meninges and about the central canal but no changes in the nerve cells or fiber tracts. The authors concluded that doses of 0.1 and 0.05 cc. of iodized sesame oil were tolerated by rabbits without demonstrable histologic damage to the spinal cords, although this is not an inconsiderable amount for this animal.

In 1930 Davis, Haven, and Stone [8] reported a series of experiments on dogs in which they first performed a laminectomy in the upper dorsal region, inserting a piece of soft rubber drain between the dura and the bony wall of the spinal canal; then 1.5 cc. of iodized poppyseed oil 40 per cent was injected by cisternal puncture and was allowed to run down to the level of the artificially produced subarachnoid block. At varying intervals after injection the dogs were killed. The gross examination of the spinal cords revealed a normal appearance in all but 1 case, in which there was hemorrhagic pachymeningitis on the anterior aspect of the cord immediately above the subarachnoid block. Microscopically the changes were similar in all cases, the degree of abnormality being directly proportional to the length of time the iodized oil had been present. The most common change was a pronounced leptomeningeal reaction, consisting of mononuclear and polymorphonuclear cells. Immediately

7. Peiper, H., and Klose, H.: Ueber die Grundlagen einer Myelographie, Arch. f. klin. Chir. **134**:303-387, 1925.

8. Davis, L.; Haven, H. A., and Stone, T. T.: The Effect of Injections of Iodized Oil in the Spinal Subarachnoid Space, J. A. M. A. **94**:772-777 (March 15) 1930.

above the level of subarachnoid block there were many vacuoles of various sizes surrounded by thickened leptomeninges and containing material which was thought to represent encysted iodized oil. The anterior horn cells were decreased in number, and the remaining cells showed degenerative changes. There was an increase in the vascular structures of the anterior horns, and the anterior spinal vessels were thrombosed in many instances. In most cases the central canal was distended with cellular elements, chiefly small round cells. No mention is made of any pathologic observations on control animals. The authors concluded that the injection of iodized oil into the subarachnoid space is to be regarded as a dangerous procedure.

In 1931 Bruskin and Propper [9] reported experiments in which 10 dogs were subjected to cisternal injections of 2 cc. of 40 per cent iodized sesame oil. The animals showed no clinical symptoms and were killed at the end of two months. There were no gross changes in the cords or meninges. Microscopic examination showed pronounced changes in the meninges, consisting of acute inflammatory reactions, adhesions between dura and arachnoid and formation of encysted oil globules, which they called "oleogranulomas." There were perivascular infiltrations, congestion of the veins and small hemorrhages into the gray and white matter of the cord. Areas of necrosis and neuronophagia were present in the gray matter. In places where the meninges had reacted most violently the cord itself was least affected. The authors expressed the opinion that the mechanism of these reactions was splitting of the iodized oil into iodine and noxious oils, the former producing the reaction. This is a slow process and produces a chronic irritation, which may continue for months.

Thus it has been repeatedly demonstrated that the presence of an iodized oil in the spinal subarachnoid space is capable of producing chronic leptomeningitis, leading to encystment of oil globules, vascular changes, consisting of congestion, hemorrhages, thromboses and capillary proliferation, and necroses within the gray matter. As Peiper and Klose [7] demonstrated, however, the severity of the reaction is directly proportional to the amount of iodized oil injected, small amounts being tolerated without any significant pathologic effects. In criticism of other experimental studies which have been reported, it must be said that this fact has been ignored. Davis, Haven and Stone used 1.5 cc. of iodized poppyseed oil 40 per cent for dogs weighing from 14 to 18 Kg. With body weight as a basis for comparison, this dose represents the equivalent

9. Bruskin, J., and Propper, N.: Experimentelle Myelo-Encephalographie an Hunden und über den Einfluss von Iodipin und Lipiodol auf das Rückenmark, Gehirn, und dessen Häute, Ztschr. f. d. ges. exper. Med. **75**:34-55, 1931.

of between 5.4 and 6.8 cc. for an average man weighing 150 pounds (68.2 Kg.). Although 5 cc. is often instilled in the lumbar subarachnoid space for demonstration of ruptured intervertebral disk, the maximum amount ordinarily injected into the cisterna magna for demonstration of subarachnoid block is 2 cc. The amount of oil used in their experiments was, therefore, between two and a half and three and a half times the equivalent amount used clinically. The same criticism applies to the work of Bruskin and Propper, who used 2 cc. routinely in dogs whose weight varied between 2 and 10 Kg. While it may be desirable to use these excessive amounts to produce definite pathologic lesions, it is obvious that the results cannot be considered applicable to clinical practice.

PRESENT INVESTIGATION

In an effort to correct this error, a series of experiments was carried out in which an attempt was made to adjust the size of the injection to the size of the animal.

Six medium-sized dogs, ranging in weight from 7.3 to 10.9 Kg., were used. These animals had all been kept in cages in the animal quarters for various lengths of time and were well adapted to this mode of life before the experiments were begun. The oil used was iodized poppyseed oil 40 per cent, obtained in standard 1 and 5 cc. sterile ampules. Assuming that the maximum dose used clinically for an average man weighing 150 pounds (68.2 Kg.) would be 5 cc., the calculated per kilogram dose would be 0.073 cc. Accordingly, the dogs were given an equivalent amount on the basis of their body weight. It is appreciated that weight is not an accurate index of comparison between dog and man with respect to the volumes of the respective subarachnoid spaces. It is, however, probably the best index which can be arrived at without resorting to elaborate biometric determinations, and for practical purposes may be used. In every case an initial attempt was made to inject the iodized oil into the cisterna magna with the animal under anesthesia induced with sodium amytal, sterile technic being employed. As soon as the injection was completed, the needle was withdrawn, and the dog was held in the upright position for a few minutes in order to permit the oil to run down the subarachnoid space. The dog was then examined under the fluoroscope to check the position of the oil. In those cases in which the first injection proved unsatisfactory, a second injection was made by the lumbar route. The dogs were then observed from time to time for the possible development of symptoms and were killed after intervals varying from fourteen days to three hundred and fourteen days. Before killing the dogs roentgenograms were taken to verify the presence and determine the position of the oil. The animals were killed with an overdose of ether. The spinal cords were immediately removed and placed in the appropriate fixatives. After fixation, the cords, with their meninges intact, were cut and examined grossly. Blocks of formaldehyde-fixed tissue were selected from various levels for staining with hematoxylin and eosin, Verhoeff's method for connective tissue and the Pal-Weigert technic for myelin. Other blocks, fixed in 95 per cent alcohol, were embedded in pyroxylin and used for Nissl's stain with toluidine blue. Nerve roots from the cauda equina were stained with osmic acid for myelin sheaths and by Bodian's method for nerve fiber. Frozen sections of spinal cord, selected from levels where the oil appeared most abundant in the roentgenograms, were

stained with Herxheimer's scarlet red for fat. To obtain the normal appearance of the tissue of the dog with these stains, the cords and nerve roots of 2 "control" animals were studied in a similar manner.

PROTOCOLS

EXPERIMENT 1.—A dog weighing 10.9 Kg. was given an injection of 0.8 cc. of iodized poppyseed oil into the cisterna magna. Fluoroscopic examination showed

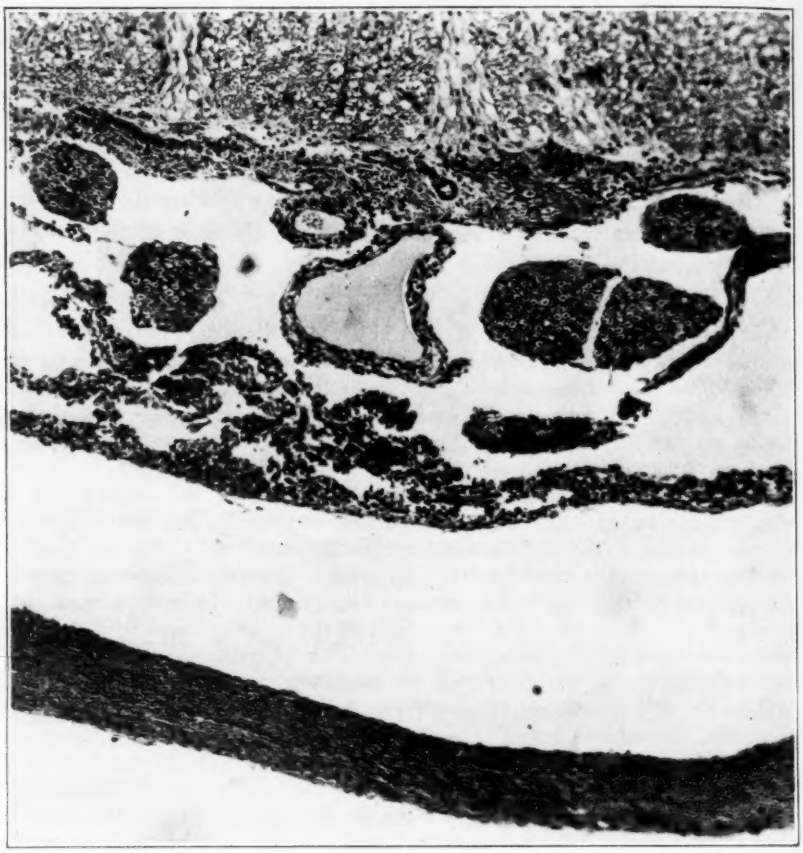

Fig. 1 (experiment 1).—Photomicrograph, showing the meninges on the ventrolateral surface of the cord at the seventh cervical level. There are massive infiltration of the pia-arachnoid membranes and perivascular infiltration. The cells are macrophages, round cells and polymorphonuclear cells. Hematoxylin and eosin stain; × 100.

that about half the oil was deposited in the basal cisterns, the rest being scattered throughout the cervical portion of the spinal canal, particularly between the fifth and the seventh cervical vertebra. The dog showed no symptoms and was killed

fourteen days after the injection. A culture of the cerebrospinal fluid was sterile. The medulla oblongata and the spinal cord were removed. Grossly no lesion or iodized oil was seen. Sections taken at the levels of the first, fourth and seventh cervical segments and stained with hematoxylin and eosin showed evidence of diffuse and moderately severe leptomeningitis (fig. 1). The inflammatory reaction, which was more intense over the ventral surface of the cord than over the dorsal surface, involved the pia-arachnoid, the adventitia of the blood vessels and some of the ventral roots. In places, massive exudates in the subarachnoid space surrounded empty spaces, which may have contained encysted oil dissolved out by the fixative. The cells were predominantly large mononuclear macrophages and round cells, but polymorphonuclear leukocytes were also present in small numbers. A section taken at the sixth thoracic level showed only a single small cell infiltration. No lesions were seen within the substance of the spinal cord. There was no evidence of thrombosis. A section of the cervical portion of the cord, stained by Herxheimer's scarlet red method, showed small globules of fat enmeshed in the arachnoid trabeculae and surrounded by inflammatory cells. A few such globules were seen beneath the pia. When examined with the polarizing microscope, this fat was found not to be doubly refractile.

EXPERIMENT 2.—A 9.5 Kg. dog received 0.6 cc. of iodized poppyseed oil by cisternal puncture. Fluoroscopic examination showed the oil to be freely movable in the subarachnoid space and spread out in droplets throughout the thoracic region. No symptoms were noted. Seventy days after injection a roentgenogram revealed iodized oil scattered between the lower thoracic region and the base of the tail. The dog was then killed. Again, on sectioning the cord, no lesions or oil could be seen on gross examination. Microscopically bands of fibrous tissue were seen surrounding the conus medullaris and the roots of the cauda equina. There was no evidence of an inflammatory reaction, although small globules of fat were demonstrated in the subarachnoid space about the periphery of the cord. The cord itself and the nerve roots were normal.

EXPERIMENT 3.—An 8.4 Kg. dog was given 0.6 cc. of iodized poppyseed oil by cisternal puncture. No symptoms developed. Ninety-one days after the injection a roentgenogram showed that the oil was scattered throughout the lumbosacral portion of the canal. The dog was then killed, and the cord was removed from the upper thoracic region to the base of the tail. Grossly no lesions or oil was visible. Microscopic study revealed no abnormality in the sections from the thoracic and lumbar levels. A section through the conus medullaris and the cauda equina showed thickening of the arachnoid septums and scattered exudates in the ventral portion of the subarachnoid space, some of these surrounding hollow spaces which may have contained the iodized oil (fig. 2). The exudates were made up entirely of large mononuclear cells and a few round cells, no polymorphonuclear cells being present. The scarlet red stain showed a large number of fat globules scattered about the cord, some enmeshed in thickened arachnoid septums. There was no abnormality of the nerve roots or of the cord itself.

EXPERIMENT 4.—A 7.3 Kg. dog received 0.5 cc. of iodized poppyseed oil by cisternal puncture. Fluoroscopy showed that the injection had been unsatisfactory. A lumbar puncture was then done and another 0.5 cc. injected. The dog showed no symptoms. One hundred and thirty-six days later a roentgenogram showed droplets of oil scattered throughout the thoracic and lumbar portions of the spine. At necropsy the cord was removed from the first thoracic segment to the base of the tail. Grossly no oil was seen. There were brownish discolorations of the dura

in the midthoracic region, suggesting the occurrence of hemorrhagic pachymeningitis. Sections from this region showed a moderate amount of cellular infiltration outside the dura and in the leptomeninges, the cells being entirely large mononuclear leukocytes. A section from the lower thoracic region showed pronounced vascular and perivascular infiltration with round cells. At the level of the cauda equina there was slight perivascular round cell infiltration. Globules of fat were present in the subarachnoid space. The cord itself and the nerve roots showed no lesions.

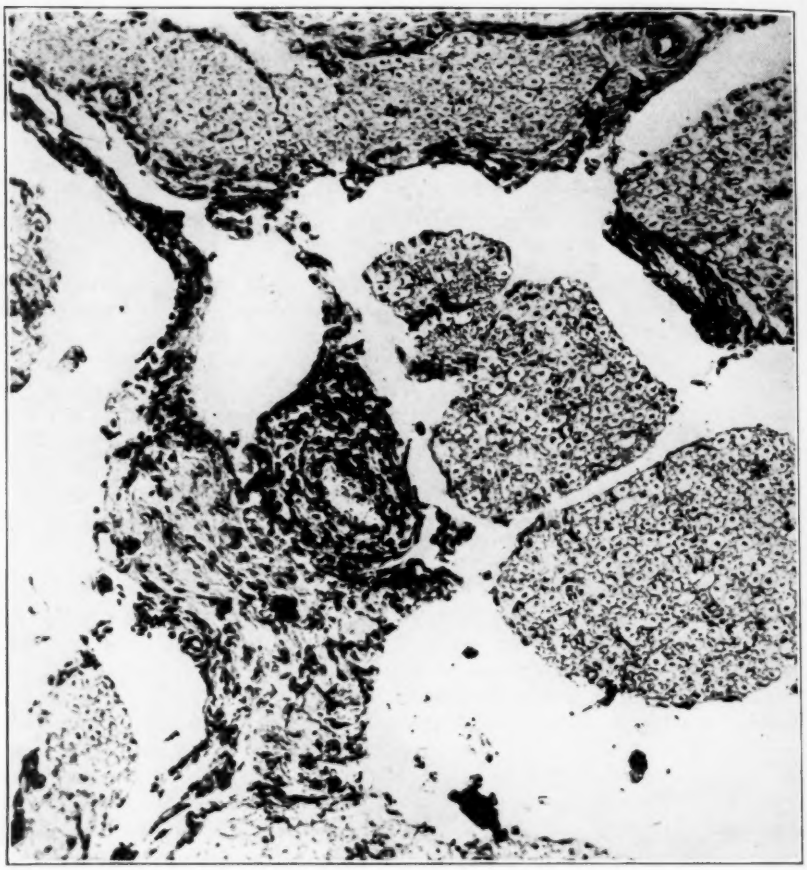

Fig. 2 (experiment 3).—Photomicrograph, showing a section of the cauda equina. There is conspicuous perivascular infiltration about a small vein, above which a hollow space is surrounded by inflammatory cells. The cells are mostly large mononuclears, but a few round cells are present. Hematoxylin and eosin stain; × 150.

Experiment 5.—A 7.5 Kg. dog was given 0.5 cc. of iodized poppyseed oil by cisternal puncture. Fluoroscopic examination two days later revealed all the oil to be deposited in the cisterna magna. Another 0.5 cc. of oil was then injected by lumbar puncture, and a roentgenogram showed this to be scattered throughout the lumbosacral portion of the canal. Two hundred and eighty-five days after the

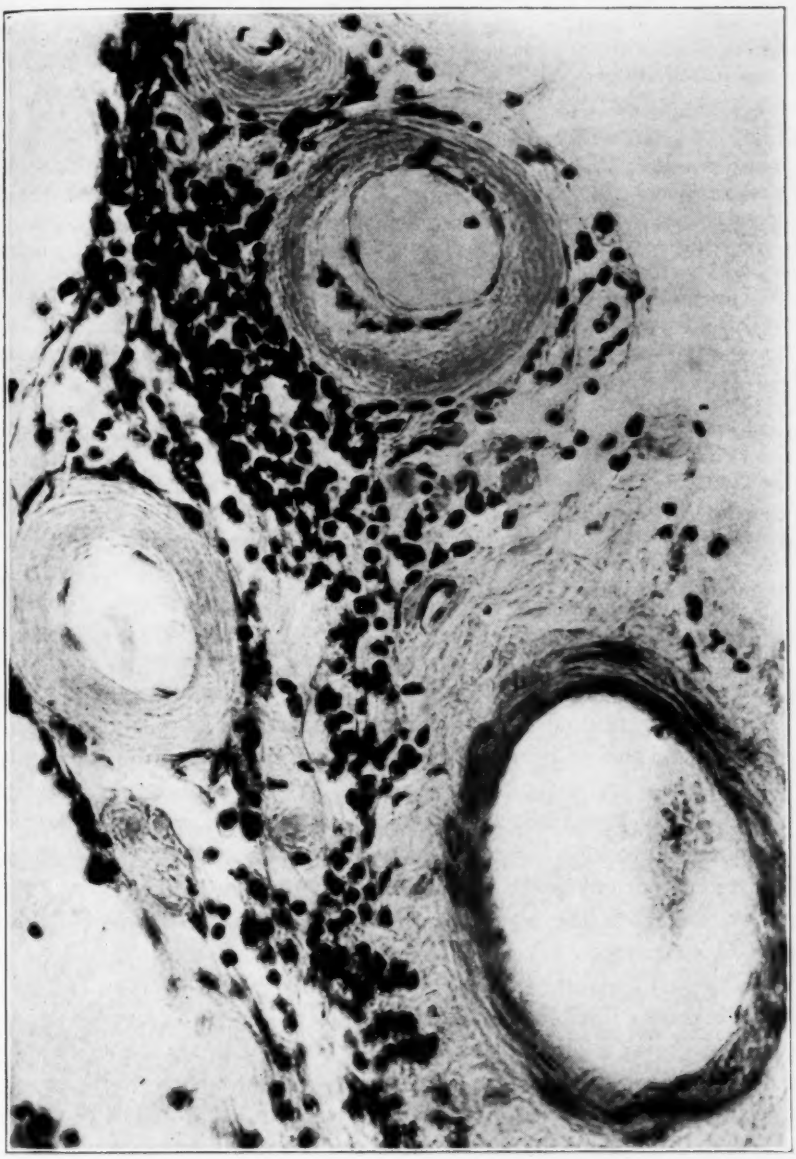

Fig. 3 (experiment 6).—Photomicrograph, showing sections of three arteries and a vein on the ventral surface of the cord at the seventh cervical level. Note the perivascular infiltration and thickening of the arachnoid septum. The cells are entirely macrophages. Hematoxylin and eosin stain; × 480.

lumbar injection the dog was killed, and the cord was removed from the mid-thoracic region to the base of the tail. Several sections of spinal cord stained with hematoxylin and eosin and with toluidine blue, as well as sections of nerve roots stained wth osmic acid and by Bodian's method for nerve fibers, showed no lesions. Small globules of fat were demonstrated in the subarachnoid space, with no reaction about them.

EXPERIMENT 6.—An 8.2 Kg. dog was given 0.6 cc. of iodized poppyseed oil by cisternal puncture. One hundred and forty-four days later a roentgenogram showed that the oil lay in the extradural space in the lower cervical and upper thoracic regions. At this time a second cisternal puncture was done, and the oil injected lodged in the basal cisterns. The dog showed no symptoms at any time. It was killed three hundred and fourteen days after the first injection, or one hundred and seventy days after the second injection. The brain and spinal cord were removed. Brownish streaks discolored the dura from the third to the eighth cervical segment. From the fourth cervical to the third thoracic level fine adhesions between the dura and the anterior wall of the vertebral canal were discovered. No iodized oil was seen. Microscopic study of the brain stem revealed no lesions except for perivascular infiltrations about the veins on the ventral surface of the medulla oblongata. Sections of the lower cervical portion of the cord revealed pronounced thickening of the arachnoid membrane and septums on the ventral aspect of the cord, with large accumulations of round cells and macrophages in the arachnoid septums and about the smaller blood vessels (fig. 3). There was no thickening or inflammation of the dura. Sections showed no lesions within the cord. Herxheimer's scarlet red stain demonstrated the presence of fat globules in the subarachnoid space in the cervical region.

COMMENT

It is significant that the pathologic changes demonstrated in these experiments were limited to inflammatory reactions involving the leptomeninges and the walls of blood vessels coursing through the subarachnoid space. This leptomeningitis was most acute and most extensive in the dog which was killed at the end of fourteen days. In the second experiment adhesions about the conus medullaris and the cauda equina constituted the only abnormal finding. In the third experiment there was thickening of the arachnoid septums, and scattered accumulations of mononuclear cells were seen among the roots of the cauda equina; in places the arrangement of these exudates suggested that they had surrounded small collections of iodized oil. In the fourth experiment there was evidence of a chronic inflammatory reaction in the leptomeninges and, also, outside the dura. The fifth experiment was entirely without significance. The results of the sixth experiment could not be evaluated accurately because of the double injection and the uncertainty as to the position of the oil. Here, again, however, the appearance was that of chronic arachnoiditis of mild degree. In every case the lesions were most pronounced in the ventral meninges, suggesting the effect of gravity on the iodized oil. None of the dogs showed microscopic evidence of an

inflammatory process, degenerative change or vascular disturbance within the cord. In no case did the nerve roots show degeneration of myelin or nerve fibers. Finally, there was no evidence of pressure on the cord resulting from the presence of encysted oil globules.

While the results of these experiments are not striking, I believe it important to emphasize the relatively benign nature of the lesions as an antidote to the alarming results reported in animal experiments by other investigators. Actually, my observations are in keeping with those of Peiper and Klose, who found that small injections of iodized oil produced only inflammatory changes, and with the bulk of clinical experience, which teaches that the only consistent reaction to intrathecal injections of iodized oil is immediate sterile leptomeningitis. In most cases in which late harmful effects have been reported, the damage can be traced to the injudicious use of iodized oil in patients with preexisting inflammatory conditions or to the employment of improper preparations of iodized oil. I believe that the essential difference between the results reported here and those of other investigators lies in the amount of iodized oil injected. The fairly constant occurrence of leptomeningitis having been demonstrated, it is to be expected that the more iodized oil is present, the more severe the effects will be. Larger injections of iodized oil could produce harmful effects in two ways: (1) by liberating larger amounts of iodine and fatty acid, and (2) by providing larger masses of foreign material for encystment, with the possibility that such masses might produce pressure effects. This should constitute a warning to clinicians not to exceed the customary amounts of iodized oil and to use as little as necessary for adequate demonstration of the suspected lesion. Furthermore, in the diagnosis of ruptured intervertebral disk, which requires the injection of a relatively large amount of iodized poppyseed oil, an attempt should be made to aspirate the oil on completion of the roentgenographic examination, using the technic described by Kubic and Hampton [10] and by Woodhall.[11]

SUMMARY

An experimental study of the pathologic effects of iodized poppyseed oil 40 per cent injected intrathecally in a series of 6 dogs is reported. The amount of oil to be injected was carefully adjusted to the size of the animal so that it should be comparable to the maximum amount in clinical use. The animals were killed at intervals varying from fourteen to three

10. Kubic, C. S., and Hampton, A. O.: Removal of Iodized Oil by Lumbar Puncture, New England J. Med. **224**:455, 1941.

11. Woodhall, B.: Aspiration of Lipiodol Injected for the Diagnosis and Localization of Ruptured Intervertebral Discs, North Carolina M. J. **2**:655-657, 1941.

hundred and fourteen days after injection. In 5 cases examination of the spinal cord revealed evidence of an inflammatory process involving the leptomeninges and the spinal blood vessels. The reaction tended to be more acute in animals killed early than in animals killed late. In no case was there any evidence of a lesion within the cord. In 1 experiment there was no reaction. These results are at variance with those reported by other investigators on the basis of animal experiments, and it is suggested that this difference is related to the relative amount of iodized oil injected.

Dr. R. W. Graves and Dr. Barnes Woodhall assisted in conducting the experiments.

919 Monmouth Avenue.

USE OF TESTOSTERONE PROPIONATE IN TREATMENT OF INVOLUTIONAL PSYCHOSIS IN THE MALE

EUGENE DAVIDOFF, M.D.
AND
GERALD L. GOODSTONE, M.D.*
SYRACUSE, N.Y.

In this communication we report the results obtained from the administration of androgen to 20 male patients who exhibited signs of the involutional psychosis. Testosterone propionate [1] was employed. This substance resembles the natural androgen in all respects.

During the first week the patients received 70 to 75 mg. of testosterone propionate, injected intramuscularly. Ten milligrams was administered daily to 15 patients. Five patients had injections of 25 mg. three times weekly. For the next month the patients received 30 to 50 mg. weekly. When sufficient improvement was not obtained, a maintenance dose of 20 to 25 mg. was administered for another month. With 6 patients the dose was again increased from 50 to 75 mg. during the second month. The average duration of treatment was six weeks. Only 1 patient received treatment for more than three months. The progress of 15 of these patients has been followed for more than one year.

Involutional psychoses were subdivided into mild, moderate and severe types.[2] In the mild form symptoms were similar to the psychoneurotic manifestations observed in the involutional syndrome without psychosis and associated with gonadal deficiency. In the moderately severe form androgenic deficiency was a precipitating factor, but other manifestations of psychogenic, somatic, autonomic or endocrine origin were present. The symptoms manifested in this type were generally more protracted than those in the mild type. In the severe form the involutional symptoms colored or were superimposed on preexisting severe personality deviations or definitely established abnormal mental states of psychogenic or organic origin.

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* Dr. Goodstone is now serving as first lieutenant in the Medical Corps of the United States Army.

1. The preparation, known as oreton, was furnished by Dr. Max Gilbert, Schering Corporation, Bloomfield, N.J.

2. Brew, M. F., and Davidoff, E.: The Involutional Psychoses: Psychotic Personality and Prognosis, Psychiatric Quart. **14**:412-434 (April) 1940.

RESULTS

The results of androgenic therapy of male involutional psychosis are listed in table 1. Thirteen of 20 patients (65 per cent) were improved. In analyzing the results, it will be seen that all of the 3 patients with mild and 8 of the 10 patients with moderately severe psychoses were beneficially affected. However, the degree of improvement in the latter group was not as pronounced. A longer period was necessary to produce a favorable effect, and remissions were more likely to occur. The severe type did not respond well to androgenic therapy. Only 2 of the 7 patients with this form were slightly improved.

TABLE 1.—*Results Obtained from Administration of Testosterone Propionate to Twenty Men With Involutional Psychoses*

	Number of Patients	Number Much Improved	Number Improved	Total Number Improved	Percentage Improved
Mild	3	3	0	3	100
Moderately severe	10	2	6	8	80
Severe	7	0	2	2	28
Total	20	5	8	13	65

TABLE 2.—*Results Obtained in a Control Series of Forty-Eight Men Treated by Routine Hospital Procedures*

	Number of Patients	Number Much Improved	Number Improved	Total Number Improved	Percentage Improved
Mild	9	4	2	6	67
Moderately severe	23	5	8	13	57
Severe	16	0	3	3	18
Total	48	9	13	22	46

In table 2 the results obtained in the treatment of a control series of 48 patients by routine hospital procedures are outlined. Twenty-two (46 per cent) manifested improvement. It appears that the mild and moderately severe types responded better to androgenic therapy than they did to procedures previously employed but that the severe type in either series did not react favorably.

Untoward effects of varying degrees of severity were noted in all the patients. These are listed in table 3. For the most part, the symptoms were only temporary. However, in 3 patients with the severe type the untoward effects were more lasting. Two of these patients, after

manifesting increased agitation, attempted suicide. One exhibited increasing depression and showed signs of vasomotor collapse during the therapy.

The involutional syndrome in the male differs in certain respects from the symptom complex in the female. Psychologic manifestations in the involutional period without the presence of a definite psychosis occur more frequently among women. Mild involutional psychoses which resemble the normal menopausal symptoms and appear to have a rather intimate association with the climacterium are encountered often in females. Because of the complex pelvic, endocrine and autonomic organization, some of the psychologic concomitants may be recognized earlier, and milder agitated depressions arising from the emotional tensions in this period of life are more frequent among women.

TABLE 3.—*Untoward Effects of Androgen Therapy*

Physiologic	No. of Cases	Psychologic	No. of Cases
Generalized cutaneous and vasomotor manifestations	19	Increased erotism	13
Headache	15	Increased restlessness	7
Pallor	6	Increased excitement or agitation	4
Weakness	5	Increased depression or apathy	4
Nausea or vomiting	4	Diminished potency	3
Pruritis ani	3	Suicidal attempts	2
Vertigo	3	Homosexual advances	2
Abdominal cramps	2	Masturbation	2
Collapse	1		

A larger percentage of the moderate forms of this psychosis are observed among men. Apathy or emotional instability associated with impotence or early organic changes in the central nervous system is more often found. Since the male patients exhibiting symptoms of involutional psychoses are generally older than the women, accompanying arteriosclerotic, senile or presenile changes occur more often. Spontaneous improvement was noted in 46 per cent of the male control series and in 42 per cent of the female control group. Sixty-five per cent of the male patients were benefited by androgenic therapy, and 62 per cent of the females were improved by estrogenic therapy.

Within certain limits the use of testosterone propionate as a therapeutic test may be of some diagnostic value. It may differentiate those milder mental states [3] occurring in the male involutional period as a result of androgen deficiency from those disturbances in which the

3. Werner, A. A.: The Male Climacteric, J. A. M. A. **112**:1441-1443 (April 15) 1939.

gonadal factor is of minor importance [4] and in which other organic or psychogenic components predominate. The use of estrogen therapy in the female for the same purpose has been recommended.[5]

REPORT OF CASES

CASE 1.—*Mild type of involutional psychosis in the male.*

H. B., aged 46, had a negative family history with respect to the presence of nervous or mental disease.

Personal History, Development and Previous Adjustment.—The patient's birth and early development were normal. He had a good record in school and completed three years of college. He was a veteran of World War I. At the age of 30 he married and made a good adjustment in his marital life. He had 2 children. For the past fifteen years he has been manager of a general store.

Personality.—He was described as friendly, very conscientious and a hard worker, but he had some outside interests. However, he avoided taking responsibility in crisis situations and depended on his brother or his wife for most of the decisions in regard to business and family matters. His wife was apparently the more aggressive, and she frequently told him that she thought people were imposing on him.

Onset of Psychosis.—The onset was gradual and of about one year's duration. In the past twelve months signs of depression and emotional instability had slowly developed. He complained of impotence and lost 40 pounds (18 Kg.) in weight. For the past month he had cried constantly. He said that he was "no good" and that he had cheated his family. He threatened suicide. On one occasion he took a rifle to his room and on another he took a rope to bed with him. On each occasion he gave a great deal of advance notice of his suicidal intent. He had been unable to sleep and stated that he would have to "end it all" because of the scandal that would ensue if his past guilty behavior was discovered.

Course of Illness.—On admission to the hospital, on Nov. 11, 1939, he was anxious, restless and tearful. He spoke of an affair he had had with a woman before his marriage. He stated that she was pressing him for money, that she claimed she was pregnant and that she had been blackmailing him. Since he had concealed all this from his wife, he blamed himself for the fact that his wife and family would suffer because he had given this woman so much money. He was only moderately agitated, but was easily upset and continued to express ideas of guilt, sin and self destruction. The sensorium was intact.

Physical examination revealed only a mild degree of arteriosclerosis. His blood pressure was 150 systolic and 80 diastolic. Except for external hemorrhoids, no significant condition was present.

Treatment.—He received 70 mg. of testosterone propionate the first week and 40 mg. the second week and was kept on a maintenance dose of 30 mg. for the next three weeks.

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4. Barahal, H. S.: Testosterone in Male Involutional Melancholia, Psychiatric Quart. **12**:743-749 (Oct.) 1938. Zeifert, M.: Massive Dose Testosterone Therapy in Male Involutional Psychosis, ibid. **16**:319-332 (April) 1942.

5. Davidoff, E., and Goodstone, G. L.: The Endocrine Treatment of Involutional Psychosis, read at the Up-State Interhospital Conference, Utica, New York, April 1941. Brew and Davidoff.[2]

Result.—During the treatment he mainfested rapid improvement. After a month had elapsed his depression, suicidal intent and agitation disappeared. He was discharged from the hospital as much improved.

CASE 2.—*Moderately severe form.*

In the case of L. G. K., aged 65, nothing is known of the family history, as his mother died during his birth and he was adopted soon after.

Personal History, Development and Previous Adjustment.—The patient had been a sickly infant. At the age of 9 he learned that he was an adopted child; he was upset by this discovery and was rather sensitive about it. About that time his foster father, to whom he was much attached, died. However, he developed normally in the adolescent period. He married at the age of 25. His relationship with his wife was congenial. They had no children, although his wife was pregnant on three occasions, but each time she was delivered of a dead infant. For the past thirty years he had worked steadily as a directory clerk in a local postoffice. Nine years prior to his admission, after the death of an 80 year old man in a car accident which occurred while he was driving, he became somewhat upset and manifested neurotic symptoms. He complained of inability to swallow, somatic difficulties and train sickness. After this he became more self centered, suggestible, irritable and less desirous of the companionship of his wife. He continued to work and apparently overcame most of these symptoms, except that he appeared anxious at times.

Personality.—He was described as fairly sociable but pessimistic, sensitive and worrisome. It was noted that he had a restricted range of interests and led a routine existence and that he became irritable and ill at ease if his daily program was changed in any way. He did not like to meet new situations.

Onset of Psychosis.—Four months prior to admission he became agitated, fearful and more anxious than usual. One of his assistants was found stealing small sums of money from the mail. He felt that he was in some way implicated in these thefts. He became increasingly agitated and restless, thought that the police were going to arrest him, complained of insomnia and paced the floor constantly.

Course of Illness.—On his admission to the hospital, on April 19, 1940, he was greatly depressed and agitated and expressed ideas of impending danger and ruin. He stated that he was constantly being watched by the postal authorities, that people were talking about him, saying that he should go to jail, and that there was no hope for him. After signing a voluntary application so that he could remain longer in the institution, he stated that he had been forced to sign a declaration of guilt. He continued to express suicidal ideas and delusions of guilt. Insight was impaired, but the sensorium was intact.

Physical examination revealed moderate arteriosclerosis of the retinal and peripheral vessels. His blood pressure was 170 systolic and 90 diastolic. He was somewhat undernourished.

Treatment.—The patient received 70 mg. of testosterone propionate the first week, 40 mg. the second week and a maintenance dose of 30 mg. for the next six weeks.

Result.—He responded slowly to therapy and had one setback during the treatment. After two months, however, he seemed much improved, although he was still potentially suicidal and complained of impotence. Six months after discharge, follow-up study revealed that he had recovered completely. The last progress note stated that he was making a fair adjustment at that time.

CASE 3.—*Severe type.*

W. R., aged 51, had no history of nervous or mental disease in the direct or the collateral lines.

Personal History, Development and Previous Adjustment.—The patient had not suffered from any childhood diseases. Despite his good background and an average mentality, he failed to take advantage of his educational opportunities. He showed little interest in school, reached the eighth grade at the age of 15 and preferred to stay at home with his mother, to whom he was much attached. He manifested no special adaptabilities. His occupation was that of chauffeur, but because his parents were in comfortable circumstances, he had no incentive to work steadily. He devoted most of his time to taking care of his invalid mother and was with her constantly for ten years prior to her death, in 1930. Soon after, his mood became hopeless and despondent and he spent many hours at her grave. He then lived with his histers and maiden aunts, remained aloof from every one else, but apparently made a superficial adjustment in this restricted environment; since he was not communicative, no signs of a definite psychosis were noted by the family until the onset of the present illness.

Personality.—In addition to his excessive mother attachment, he was quiet, seclusive and finicky; he took no interest in the opposite sex, remained single and had practically no friends outside his immediate family. He was described by his sisters as "different"; he had a tendency to drink by himself but manifested no other bad habits. He was considered a very good boy who never gave any trouble.

Onset of Psychosis.—One month prior to admission he gave up his job, became disturbed, tense and fearful, expressed the belief that something was wrong with his prostate and genitals and complained of pain in his heart. Several physicians told him that his physical condition was normal. Shortly before entering the hospital he began to wring his hands and talked of cutting out his tongue and doing away with himself.

Course of Illness.—On his admission to the hospital, on Aug. 24, 1939, he was exceedingly apprehensive and severely agitated and expressed auditory hallucinations, nihilistic delusions and ideas of reference. He stated that his condition was hopeless, that he had been sinful and guilty and that he wanted to die. Most of the time he was preoccupied and somewhat uncommunicative. Insight and judgment were lacking, but the sensorium was intact.

Physical examination revealed nothing significant except slight enlargement of the prostate.

Treatment.—The patient received 70 mg. of testosterone propionate the first week, 40 mg. the second week and 30 mg. the third week.

Result.—After the third week of therapy he became exceedingly agitated, restless and fearful. He surreptitiously obtained a razor blade and with this inflicted three deep lacerations on the anterior aspect of his neck, severing the inferior thyroid vein. He lost a great deal of blood, but his life was spared by prompt ligation of the vessel. After six weeks' residence in the hospital, he was committed to a larger state hospital for continued care. He has shown little or no improvement at this institution.

SUMMARY

Twenty male patients suffering from involutional psychoses were treated with testosterone propionate, administered intramuscularly for a period of from six weeks to three months.

Sixty-five per cent of the patients responded well. In the control group treated by procedures previously employed, only 46 per cent improved. The best results were obtained with the mild and moderately severe types. The severe type did not respond well to androgenic therapy and may represent a different clinical entity from the other two.

The therapeutic test with testosterone proprionate may be of some diagnostic value in differentiating the milder type, in which androgenic deficiency is an important etiologic factor, from the more severe type, in which other psychologic or organic factors predominate.

Willard State Hospital.

FATALITY FOLLOWING INTRAVENOUS ADMINISTRATION OF MAGNESIUM SULFATE

REPORT OF A CASE

MILTON ROSENBAUM, M.D.
AND
SAMUEL D. LIPTON, M.D.
CINCINNATI

Since the introduction of convulsive shock therapy, various methods have been used to prevent the traumatic complications. Recently Yaskin [1] described favorable results in preventing these complications by the use of magnesium sulfate as a curare-like agent. He injected intravenously 25 to 30 cc. of a 25 per cent sterile aqueous solution of magnesium sulfate as rapidly as possible. The injection was followed immediately by cutaneous flushing, with a concomitant subjective complaint of a marked sensation of "heat," heaviness of the eyelids, bilateral ptosis, weakness of the neck muscles, slurred speech and weakness of the extremities. This syndrome was produced in one to three minutes, and at the height of the reaction metrazol was injected, with a resulting "softened" convulsion. The peripheral muscular paresis usually disappeared within three to six minutes after the effect was reached. Yaskin reported on 256 magnesium sulfate–metrazol treatments administered to 23 patients, ranging in age from 18 to 64 years, with no deleterious results and no traumatic complications. Because of these favorable results and because the method is simple and inexpensive, it was decided to use it in the psychiatric service of the Cincinnati General Hospital.

The first patient to receive the treatment was a man aged 32 who was suffering from a depression. He had improved under treatment with metrazol and received an intravenous injection of 30 cc. of magnesium sulfate with the last injection of metrazol. A "softened" convulsion resulted.

The second patient was a white woman aged 32, who was also depressed. She received three separate injections of 25 cc. of magnesium

From the Psychiatric Department of the University of Cincinnati College of Medicine, and the Psychiatric Service of the Cincinnati General Hospital.

1. Yaskin, H. E.: Prevention of Traumatic Complications in Convulsive Shock Therapy by Magnesium Sulfate, Arch. Neurol. & Psychiat. **46**:81-85 (July) 1941.

sulfate followed by 5 cc. of metrazol, without any diminution in the intensity of the resultant convulsion. Indeed, she suffered dislocation of the mandible after the first treatment. The third patient died after an injection of magnesium sulfate.

REPORT OF CASE

A spinster aged 60, white, was admitted to the psychiatric service of the Cincinnati General Hospital on Aug. 11, 1941, after a suicidal attempt by ingestion of ammonia.

History.—The patient had been entirely well until one month before admission, when she gradually became depressed. The depression was characterized by agitation, feelings of guilt, loss of appetite, loss of weight and psychomotor retardation. The symptoms gradually increased in severity, culminating in the attempt at suicide on the morning of admission.

Mental Status.—The patient was obviously depressed; she was quiet and seclusive and showed pronounced psychomotor retardation. There was no evidence of any intellectual defect.

Physical Examination.—Except for emaciation (weight 78 pounds [35.4 Kg.]) and a mild chemical burn (due to ingestion of ammonia) about the mouth, the physical examination revealed essentially nothing of significance. The blood pressure was 120 systolic and 80 diastolic. The neurologic examination gave negative results.

Laboratory Examination.—The red blood cell count was 4,210,000 and the hemoglobin 12.4 Gm. per hundred cubic centimeters. The white blood cell count was 7,900, and the differential count revealed 58 per cent polymorphonuclears, 40 per cent lymphocytes and 2 per cent mononuclears. The urine was normal, and the urea nitrogen of the blood measured 19 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative. An electrocardiogram was normal. Roentgenograms of the chest revealed no abnormality of the heart or lungs. Anteroposterior and lateral roentgenograms of the dorsolumbar portion of the spine showed nothing abnormal except moderate generalized demineralization of the whole bony framework, which was compatible with the patient's age. Fluoroscopy of the esophagus with barium sulfate showed no evidence of stricture.

Diagnosis.—The diagnosis was "late life depression."

Course.—Since the general physical condition of the patient was fairly good, it was decided to treat her with metrazol. Because the emaciation and generalized demineralization of the bony framework increased the possibility of a traumatic complication, it was thought advisable to attempt to reduce the severity of the convulsions by the use of magnesium sulfate. The technic described by Yaskin was followed.

Treatment.—The patient received seven injections of magnesium sulfate and metrazol. A 25 per cent solution of magnesium sulfate was used and was injected as rapidly as possible through an 18 gage needle. The dose was gradually increased from 15 cc., in the first treatment, to 25 cc., in the sixth treatment, without satisfactorily softening the convulsion. The patient seemed to suffer no ill effect from the magnesium sulfate.

In the seventh treatment the dose was therefore increased to 30 cc. Immediately after the injection there were contraction of the muscles of the neck

and flexion of the arms, almost as if a convulsion were about to start. Thirty seconds after the end of the injection there were two or three inspiratory gasps, and then respiration ceased. At this time the patient was pulseless; no heart sounds could be heard and no blood pressure obtained. The patient was given in rapid order 10 cc. of 5 per cent calcium chloride, coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) and 7 cc. of metrazol intravenously through the original needle. Artificial respiration was started about forty seconds after the end of the initial injection and was continued for fifteen minutes, without avail.

Anatomic Diagnosis.—The cause of death was not determined. Autopsy revealed moderate atherosclerosis of the aorta and coronary arteries, moderate myocardial fibrosis and acute passive congestion of the lower lobe of the right lung and of the gastroenteric tract. The gross appearance of the brain was within normal limits. With the exception of a small papilloma of the right choroid plexus, no abnormalities were noted on sectioning the brain.

Histologic Diagnosis.—Microscopic examination revealed (1) myocardial fibrosis with toxic myocardosis and fatty invasion of the myocardium; (2) acute passive congestion of the liver, and (3) petechial hemorrhages in the small intestine.

COMMENT

The sudden fatality encountered in this case led us to search for the mechanism responsible for the death. As has been noted, the autopsy observations were not specific. The rapidity with which death occurred pointed to sudden cardiac arrest. This diagnosis was also favored by the fact that within thirty seconds after the injection no pulse, cardiac sounds or blood pressure could be obtained. In death due to respiratory failure one would not expect such a rapid cessation of cardiac function.

Many authors have called attention to the fact that the injection of magnesium salts is followed by a fall of blood pressure and have assumed that the latter is due to the concomitant peripheral vascular dilatation.[2] In support of this is the well known clinical observation of "intense heat," redness of the skin and pronounced sweating following injection of magnesium sulfate. Winkler and his associates [2b] found that the intravenous injection of magnesium sulfate in dogs at a slow, uniform rate produced (1) a fall in blood pressure associated with cutaneous dilatation (at a concentration of 3 to 4 mg. of magnesium per hundred cubic centimeters of serum); (2) partial, followed by complete, neuromuscular block with arrest of respiration (12 to 30 mg. of magnesium per hundred cubic centimeters of serum), and (3) cardiac block and, finally, cardiac arrest at concentrations considerably above

2. (*a*) Hoff, H. E.; Smith, P. K., and Winkler, A. W.: The Relation of Blood Pressure and Concentration in Serum of Potassium, Calcium and Magnesium, Am. J. Physiol. **127**:722-730 (Nov.) 1939. (*b*) Winkler, A. W.; Hoff, H. E., and Smith, P. K.: Cardiovascular Effects of Potassium, Calcium, Magnesium, and Barium, Yale J. Biol. & Med. **13**:123-132 (Oct.) 1940.

those at which spontaneous respiration ceased. They also stated that the actual danger of its administration to man results chiefly from neuromuscular paralysis. However, in another series of experiments it was pointed out that in 3 of 11 dogs respiratory and cardiac arrest occurred simultaneously. No satisfactory explanation of this phenomenon was offered.[3]

Smith, Winkler and Hoff [3] found that injection of magnesium sulfate depresses all parts of the conduction system of the heart, but they could not explain the terminal cardiac arrest which always occurs if the concentration of magnesium is high enough, since in most instances the last beats show a well defined and vigorous systole. They assumed a direct toxic action of magnesium on the myocardium itself to explain the terminal cardiac arrest.

Hay, in 1882,[4] reported on a series of experiments on dogs and cats showing that magnesium sulfate was much more toxic when injected rapidly than when injected slowly. A 7.25 Kg. dog was instantly killed by a rapid intravenous injection of 3 cc. of a 20 per cent solution of magnesium sulfate, but if the magnesium sulfate was given slowly, a much greater amount could be injected before the animal died. Thus, 1.5 cc. of a 10 per cent solution of magnesium sulfate killed a cat when injected quickly, but 6 cc. of the same solution injected over a twenty minute period was not fatal.

Following Yaskin's technic,[1] we have given intravenous injections of 25 to 30 cc. of 25 per cent magnesium sulfate to a group of 8 patients. In 3 instances Dr. David I. Abramson measured the peripheral blood flow in the leg and hand by the venous occlusion plethysmograph method.[5] At this time we wish to mention briefly a few observations pertinent to a discussion of this case.

All subjects experienced pronounced signs and symptoms of cutaneous peripheral vasodilatation, despite the fact that in 3 of them no fall in blood pressure occurred. In 1 of the 3 subjects in whom the peripheral blood flow was recorded, a significant increase in flow occurred. In this patient there was also a precipitous fall in blood pressure, but the blood flow continued to increase after the blood pressure returned to normal.

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3. Smith, P. K.; Winkler, A. W., and Hoff, H. E.: Electrocardiographic Changes and Concentration of Magnesium in Serum Following Intravenous Injection of Magnesium Salts, Am. J. Physiol. **126**:720-730 (July) 1939.

4. Hay, M.: Action of Saline Cathartics, J. Anat. & Physiol. **16**:243-282, 1882.

5. (*a*) Abramson, D. I.; Zazeela, H. I., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man: I. Criteria for Obtaining Accurate Plethysmographic Data, Am. Heart J. **17**:194-205 (Feb.) 1939. (*b*) Ferris, E. B., Jr., and Abramson, D. I.: Description of a New Plethysmograph, ibid. **19**:233-236 (Feb.) 1940.

These observations suggest that the fall in blood pressure following injection of magnesium sulfate may not be a direct function of peripheral vasodilatation, as has been generally assumed.[2] Perhaps when enough magnesium sulfate is injected rapidly there is a transitory direct action on the myocardium, with a resulting sudden decreased cardiac output, which helps to produce the sudden, precipitous fall in blood pressure.

These studies, in addition to the pertinent literature already referred to, may help to explain the death of our patient. The very rapid injection of a fairly concentrated solution of magnesium sulfate may have produced a sudden high concentration of magnesium in the serum sufficient to cause cardiac arrest by a direct toxic action on the myocardium. Certainly, the factor of individual susceptibility is important in determining the lethal dose, just as it was in the experimental animals previously cited.[3]

SUMMARY

A case is reported in which sudden death occurred after a rapid intravenous injection of magnesium sulfate. Although direct proof is lacking, it is suggested that the death was due to sudden cardiac arrest resulting from the direct toxic action of magnesium on the myocardium.

Cincinnati General Hospital.

AMPHETAMINE SULFATE IN TREATMENT OF SPASMODIC TORTICOLLIS

REPORT OF TWO CASES

ABRAHAM MYERSON, M.D.
AND
JULIUS LOMAN, M.D.
BOSTON

Spasmodic torticollis is a symptom complex generally considered to belong in the group of disorders of the basal ganglia, although its more exact focal pathology and pathologic physiology are obscure. It frequently occurs as an isolated involvement of the sternocleidomastoid muscle, but other muscle groups may manifest a similar disability, for example, the spinal groups of muscles and the muscle groups of the foot. Spasmodic torticollis, once well established, occurs at frequent intervals or may be practically constant, and finally contracture of the muscle may result so that the head is permanently fixed in an abnormal position. Pain and discomfort frequently accompany the spasms of the muscle groups.

The therapy of spasmodic torticollis has been on the whole unsatisfactory. Scopolamine and other sedative drugs have been used, without definite effect. Benefit in some cases has been reported from section of the spinal accessory and the upper cervical nerves. Any medication which offers relief of the distressing spasm should be welcome. Since amphetamine sulfate decreases rigidity in Parkinson's syndrome,[1] it occurred to us that the drug might have a beneficial effect on spasmodic torticollis.

We have had the opportunity of observing the effect of amphetamine sulfate in 2 unusual cases of spasmodic torticollis, 1 of which we have had under observation for fourteen months and the other for five months.

From the Division of Psychiatric Research, Boston State Hospital.

This study was aided by a grant from the Commonwealth of Massachusetts.

1. (*a*) Solomon, P.; Mitchell, R. S., and Prinzmetal, M.: The Use of Benzedrine Sulphate in Postencephalitic Parkinson's Disease, J. A. M. A. **108**: 1765-1770 (May 22) 1937. (*b*) Loman, J.; Myerson, P. G., and Myerson, A.: Experimental Pharmacology of Postencephalitic Parkinson's Disease, Arch. Neurol. & Psychiat. **47**:399-412 (March) 1942.

REPORT OF CASES

CASE 1.—E. P., a woman aged 26, single, was first seen at the Massachusetts General Hospital on Feb. 5, 1940. An abstract from the hospital record follows: "At about the age of 16 the patient complained of pulling of the neck. This was not severe and soon disappeared. Physical examination showed pronounced curvature of the dorsal portion of the spine. The left sternocleidomastoid muscle was hypertrophied and could be seen to contract frequently, tilting the head so that the chin was held to the right and upward. Electromyograms revealed much continuous activity over both sides of the neck, but the left sternocleidomastoid muscle showed about three times as much as the right. This activity was of the type seen in torticollis, with much spiking. A slight movement of the head increased the contraction of the left sternocleidomastoid muscle, and when the head was turned forcibly to the right, terrific contractions occurred. Examination of other organs revealed nothing significant. The patient was given eleven injections of alcohol into the muscle, with some improvement. . . . She was readmitted on Sept. 17, 1940. Lumbar puncture, done on September 21, revealed nothing abnormal."

After the patient left the Massachusetts General Hospital, the torticollis became much more pronounced and continuous. In addition, the trunk became gradually pulled forward and remained in a permanently flexed position. Her brother, a physician, gave one of us a description of her case on Nov. 20, 1940. On the basis of this account, in addition to the hospital record, a diagnosis of spasmodic torticollis, torticollis spastica cervicalis and dorsalis, was made.

As a test of the efficacy of amphetamine sulfate on her spasmodic condition, she was given by her physician, under our direction, an intramuscular injection of 30 mg. of the drug in gelatin on December 12. An astonishing improvement occurred. Within one-half hour she began to straighten up her body. The neck, which was continuously in spasm, relaxed so that she could face fully forward. This improvement continued during the day and late into the afternoon, when she was able to go in swimming. The body was held erect, and she was able to move her head in any direction without spasm. The improvement lasted eighteen to twenty-four hours, at which time there was gradual slipping back into her former condition, so that at the end of about thirty hours she had returned to her original incapacitated state. For the first few weeks after this she was given a daily injection of 30 mg. of amphetamine sulfate in gelatin. This brought about a repetition of the results first obtained. Thereafter $\frac{1}{100}$ grain (0.6 mg.) of scopolamine hydrobromide was added to the amphetamine sulfate solution. This drug seemed to add to the relaxation obtained, so that the combined medication was continued for some time. A motion picture of the patient, taken by her family physician before and after the injection, gave graphic evidence of the efficacy of the medication.

She was first seen by one of us on June 6, 1941, having received an injection of amphetamine sulfate and scopolamine hydrobromide one-half hour before her visit. Further investigation of the history elicited the fact not only that the neck and back were involved but that the muscles about the shoulder showed some rigidity. She presented some spasm of the left sternocleidomastoid muscle, although the neck was rather freely movable from side to side. There was slight spasm of the muscles of the back. There were no spasms or rigidity in the muscles of the arms.

The patient was seen again on Oct. 7, 1941. At this time examination showed that from time to time there were some involuntary movements of slight intensity of the right shoulder and of the neck, backward and slightly to the right. Spasms

occurred in the right spinal muscles. She later reported that some confusion and difficulty in focusing the eyes had developed. Omission of the scopolamine eliminated these complaints. The patient has not been seen since Oct. 14, 1941, but she has continued to report by correspondence and to have her treatment thus supervised.

In November 1941, administration of amphetamine sulfate and scopolamine by injection was discontinued. She now receives 20 mg. of amphetamine sulfate by mouth three times a day, the last dose being taken at 4 p. m. With each dose of amphetamine sulfate 1/200 grain (0.3 mg.) of scopolamine hydrobromide is also taken by mouth. She has continued to maintain decided improvement with this medication. In her last letter, she writes that although she still complains of some spasm of the neck and difficulty in raising the arms, she has maintained marked improvement. Her appetite is good, and she sleeps well. Her stools are inclined to be loose, a symptom that has been present throughout the therapy, and she has two or three bowel movements a day. Since the treatment began she has lost 7 pounds (3.2 Kg.). She ends her letter as follows: "My general nervous and mental condition has improved a good deal. For three weeks I have had a job taking care of two school children. Other than laundry and cleaning, I do everything and lead a fairly normal and active life, with effort, of course, but it is so wonderful to be able to do so much more and to be independent and self supporting for a little while, at least. I have noticed that my motions and speed in doing anything have greatly increased."

CASE 2.—D. D., a woman aged 29, single, a nurse, was first seen on Oct. 8, 1941. The past history revealed no illness suggestive of encephalitis or other infectious disease. She injured her right ankle at the age of 15. In September 1941 she had a sore throat. The following day she complained of stiffness of the neck, which soon developed into almost constant spasmodic pulling of the neck to the left, associated with pain in the muscles of the neck. Touching the neck muscles on the right side aggravated the spasm. Baking applied to the involved part increased the severity of the symptoms. A day or two after the onset of the torticollis, the patient noticed a limp in the right leg; the right toes curled under, so that she walked on the heel.

Physical examination showed that the neck was held to the left almost constantly. The right sternocleidomastoid muscle was in severe spasm. When it did relax, tapping of the muscle immediately sent it into spasm. The gait showed a decided limp, the patient setting the right foot on the heel. Examination of the right foot showed flexion spasm of all the toes. There was no other neurologic abnormality.

At this time the patient was given an intramuscular injection of 30 mg. of amphetamine sulfate in gelatin. Five minutes later she began to experience relief of the spasm of the neck. Percussion of the involved muscle now failed to elicit the spasm. Fifteen minutes after the injection the neck was practically without spasm and was freely movable. Coincident with this relief, there occurred improvement in the spasm of the right toes, so that the limp became imperceptible. Almost complete relief of the symptoms lasted for approximately two hours, followed by a gradual return of the spasm, which reached its original state six hours after administration of the amphetamine sulfate.

The patient was then placed under a regimen of 30 mg. of the amphetamine sulfate by mouth, to be taken in the morning. In order to counteract any undue stimulating effect of the drug, 1/200 grain (0.3 mg.) of scopolamine hydrobromide was also given. After two weeks of this therapy, the patient reported that she

was obtaining about 75 per cent relief from the spasm of the neck and foot, the improvement lasting well into the afternoon. At times she took an additional 20 mg. of amphetamine sulfate in the afternoon.

On Nov. 13, 1941 the patient reported that she had found it necessary to increase the dose of amphetamine sulfate in order to obtain the former degree of improvement. She was now taking 30 mg. of amphetamine sulfate at 8 a. m., 2 p. m. and 6 p. m., to each dose of which she added 1/150 grain (0.4 mg.) of scopolamine hydrobromide. Scopolamine alone, she found, gave only slight improvement. From the combination of drugs no undue stimulation was experienced. Her appetite had diminished, and she had lost 9 pounds (4.1 Kg.) since beginning the treatment. At times her sleep was impaired. This was controlled with 1 capsule (1½ grain [0.097 Gm.]) of seconal (sodium propylmethylcarbinylallyl barbiturate). The patient was asked to add nicotinic acid to the therapy on the theory that this drug might enhance the effectiveness of the amphetamine sulfate by increasing the cerebral blood flow. On November 19 the patient reported continued decided improvement on 80 to 100 mg. of amphetamine sulfate and 1/50 grain (0.12 mg.) of scopolamine hydrobromide daily, divided into three doses. She expressed the belief that the nicotinic acid, 100 mg. three times a day, enhanced the effect of the amphetamine sulfate. By itself, the former drug gave no relief from her symptoms. On November 26, the patient reported continued improvement. She stated that the nicotinic acid caused mildly uncomfortable flushing, lasting twenty minutes, which was followed by a decided feeling of well-being to a degree which was not experienced when the drug was omitted. On December 17 she reported that in order to maintain the previous degree of improvement she found it necessary to take 40 mg. of amphetamine sulfate three times a day, to each dose of which she added 1/50 grain (0.12 mg.) of scopolamine hydrobromide in order to eliminate undue stimulation produced by the amphetamine sulfate. In addition, she was taking 200 mg. of nicotinic acid with each dose of the other two drugs. On Jan. 28, 1942 the patient reported continued excellent improvement of the spasm in her neck and foot. From time to time she omitted all medication for some hours, with rapid return of the previous severe spasmodic condition of the neck and foot. When she took amphetamine sulfate alone, she felt as though she were "jumping out of her skin." She had also tried Bulgarian belladonna, 3 tablets (0.5 mg. each) three times a day, without effect on her symptoms.

Since the patient has been under treatment with amphetamine sulfate, she has lost 14 pounds (6.4 Kg.), mainly in the first six weeks, during the time when her appetite was moderately impaired. Her appetite, however, is now good. She usually sleeps well without sedation. Her bowels have not been affected. General physical examination from time to time has not disclosed any visceral effects of the medication. The heart action and blood pressure have been normal throughout the therapy. Since beginning the medication, the patient has been able to carry out many of the activities which she formerly had to discontinue.

COMMENT

The response to amphetamine sulfate in the first case (E. P.) was so dramatic that the question of hysteria was raised in the differential diagnosis. Placebos, given both intramuscularly and orally, repeatedly failed to influence the symptoms.

The rationale of the medication for spasmodic torticollis is based on experimental observation. In previous work on Parkinson's syn-

drome,[1a] the authors observed that amphetamine sulfate had a definite effect, measured objectively, on rigidity, but slight, if any at all, on tremor. Scopolamine, on the other hand, objectively influenced both rigidity and tremor. It was hypothesized that although the pathologic changes in Parkinson's syndrome reside in the basal ganglia, the rigidity and tremor are ultimately produced through "release" of the precentral cortex. Experimental data on animals indicate that interruption of a circular suppressor pathway, which runs from areas 4-S and 8-S of the precentral cortex to the basal ganglia and back to the precentral cortex, results in overactivity of the cortex, with production of involuntary movements and abnormal tone. The locus of interruption of this inhibiting pathway may be in the caudate nucleus, the globus pallidus or the thalamus.[2] There is evidence from neurosurgical therapy for athetosis and tremor, in which certain areas of the precentral cortex are extirpated, that such a functional interrelation between these cortical and subcortical structures exists.[3] Pharmacologically, according to this relationship, amphetamine sulfate directly stimulates the underactive basal ganglia, while scopolamine inhibits the relatively overactive cortex, so that the physiologic balance between the two sets of structures is partially restored. Although these two drugs are synergistic in their influence on Parkinson's syndrome and spasmodic torticollis, in management of the former condition scopolamine is usually the more effective drug. Not only is its action reenforced, but its undesirable side effects are counteracted by the amphetamine sulfate. In treatment of spasmodic torticollis, the amphetamine sulfate plays the leading role, and its overstimulating effects are counteracted by the scopolamine. The dosage of the two drugs should be properly balanced in order to obtain the synergistic action indicated.

It is interesting to note that in case 1 remarkable effects were obtained with 20 mg. of amphetamine sulfate and $\frac{1}{200}$ grain of scopolamine hydrobromide three times a day, while in case 2 it became necessary, in order to maintain the considerable improvement, to increase gradually the dose of amphetamine sulfate to approximately 50 mg. and of scopolamine hydrobromide to $\frac{1}{150}$ grain three times a day. Despite the large doses of amphetamine sulfate, no deleterious effects have been observed. Nicotinic acid appeared to be a useful adjunct

2. Bucy, P. C.: Surgical Treatment of Choreo-Athetosis, Dis. Nerv. System **3**:77-79 (March) 1942.

3. Bucy, P. C., and Case, T. J.: Athetosis: II. Surgical Treatment of Unilateral Athetosis, Arch. Neurol. & Psychiat. **37**:983-1020 (May) 1937; Tremor: Physiologic Mechanism and Abolition by Surgical Means, ibid. **41**:721-746 (April) 1939. Klemme, R. M.: Surgical Treatment of Dystonia, with Report of One Hundred Cases, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:596-601, 1942.

to the therapy in case 2, whether by central or by local effect, as a result of changes in blood flow, cannot be answered.

SUMMARY

Two cases of spasmodic torticollis which responded remarkably to amphetamine sulfate are reported. Scopolamine was used as a synergist to counteract central overstimulation of the amphetamine sulfate. Although given in large doses, no injurious effects of the latter drug were observed. In the second case nicotinic acid appeared to enhance the effect of the amphetamine sulfate.

475 Commonwealth Avenue.

520 Beacon Street.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

THE EFFECT OF SECTION OF THE MEDIAL LEMNISCUS ON PROPRIOCEPTIVE FUNCTIONS IN CHIMPANZEES AND MONKEYS. OLOF SJÖQVIST and EDWIN A. WEINSTEIN, J. Neurophysiol. **5**:69, 1942.

Sjöqvist and Weinstein sectioned the left medial lemniscus at the level of the inferior colliculus in 2 chimpanzees and 8 macaques. Subsequent histologic examination revealed that dentatorubrothalamic fibers were also damaged in 1 chimpanzee and in several macaques. Section of one superior cerebellar peduncle was performed in 2 mangabeys. Weight discrimination was taught to the chimpanzees, the mangabeys and 1 macaque as a quantitative index of proprioceptive function. Qualitative changes were estimated from clinical observations on all the animals.

Section of the medial lemniscus alone produced only a temporary reduction in proprioceptive skill. Section of the superior cerebellar peduncle alone had no significant effect on weight discrimination. Animals in which both the medial lemniscus and the crossed dentatorubrothalamic tract were damaged suffered pronounced and lasting diminution in proprioception. The authors conclude that the cerebellar projections to the thalamus may carry proprioceptive impulses when the usual route by way of the medial lemniscus is interrupted.

DRAYER, Philadelphia.

EFFECTS EVOKED IN AN AXON BY THE ELECTRIC ACTIVITY OF A CONTIGUOUS ONE. A. ARVANITAKI, J. Neurophysiol. **5**:89, 1942.

Single giant axons from Sepia officinalis were placed in tangential contact, and the transmission of changes in potential from one to the other was studied. The term "ephapse" is proposed for such a functional contact between similar structures, in place of the somewhat ambiguous description "axon-axon synapse," previously used. The stimulated axon is called "preephaptic" and the responsive one "postephaptic."

Reactions were studied with the efferent axon quiescent and with it displaying an oscillatory activity of its own. Significant factors in determining the response were found to be the shape, height and speed of propagation of the action potential of the active fiber, the geometric conditions of contact and the excitability characteristics of the receptive axon.

Normal nerves do not show interaction between adjacent fibers because of the insulating myelin and interstitial tissue and because the activity of one axon usually gives rise to triphasic currents with a final positivity which renders them relatively ineffective as stimulants. Changes in phase of these currents in the presence of injury, together with diminution in insulation by damage to myelin and interstitial tissue, permits synchronization and ephaptic phenomena to appear. The author suggests that ephaptic interactions between cell bodies, where lipid insulation is minimal, are highly probable.

DRAYER, Philadelphia.

EFFECT OF ROENTGEN RAYS ON THE PERIPHERAL NERVE OF THE RAT. ARNOLD H. JANZEN and SHIELDS WARREN, Radiology **38**:333 (March) 1942.

Experimental observations on the effect of radiation on the peripheral nerves of mammals are few. This fact prompted the authors to conduct a study of the

effects of radiation on the sciatic nerves of the rat. Their observations were followed by histologic study of the irradiated nerves.

Stock white rats were used and the sciatic nerves on both sides isolated and kept moist with Tyrode's solution. The animals were protected with shields of lead 0.2 cm. thick and the adjacent tissues with a shield of lead placed under the nerve, the thickness being 0.1 cm. for radiation in doses of 4,000 r and 0.2 cm. for radiation in doses of 6,000 to 10,000 r. The factors of radiation were 200 kilovolts, 8 milliamperes, no extrinsic filtration, a cone 5 cm. in diameter and a target nerve distance of 15.5 cm. The skin was closed, and the animals were killed at intervals of twenty-four, forty-eight, ninety-six, one hundred and forty-four and one hundred and sixty-eight hours and two, three, four, five, six, seven and eight weeks.

An hour before the rats were killed they were tested for excitability of the nerves, break shocks from the secondary coil of an inductorium being used. Both the right and the left nerve were tested, since it was found that the nerve tested second was usually the more excitable. Both cathode-descending and cathode-ascending stimuli were used, the former measuring excitability of the irradiated segment and the latter conductivity through it. The animals were killed, and the irradiated portion of the nerve was fixed and stained by various methods. The tibial nerve and two sections from the spinal cord were also taken and fixed in an appropriate manner.

None of the irradiated rats limped or showed reduction in the use of their hindlegs, except for slight reduction in activity after the operative procedure. There was little or no difference between the irradiated and the control nerve in excitability either to the cathode-descending or to the cathode-ascending break shock. Histologic studies showed no differences between the irradiated and the control nerve, their ganglia or the anterior horn neurons of the spinal cord.

Four additional groups of animals were given radiation as controls for various factors which it was felt might alter the reaction. In one group the nerve was irradiated without being isolated, and in a second group 10,000 r was given along the course of the sciatic nerve. In the third group, composed of untreated animals, the nerve was tested for excitability. None of the groups showed any essential change as compared with the nonirradiated nerves of the treated animals. In the last group 8.5 to 13 millicuries of gold radon seeds was implanted in the left psoas muscle approximately 1 cm. lateral to the fourth lumbar vertebra and about 0.4 to 0.5 cm. from the sciatic nerve roots and trunk. The animals in this group received 1,200 to 1,600 millicurie hours, or approximately 75,000 to 100,000 r. The nerves so irradiated showed definite signs of nerve injury, with loss of reaction to the stimulus of the secondary coil of the inductorium.

The authors conclude from this experiment that exposure of the peripheral nerves of the rat to roentgen rays in doses of 4,000, 6,000 and 10,000 r generated at 200 kilovolts produced no demonstrable histologic or physiologic changes. Complete degeneration of nerve and some evidence of degeneration of sensory neurons resulted from exposure to 1,200 to 1,600 millicurie hours of gamma radiation. Nerve tissue is extremely resistant to radiation.

KENNEDY, Philadelphia.

FITNESS, FATIGUE AND RECUPERATION. F. A. HELLEBRANDT and P. V. KARPOVICH, War Med. **1**:745 (Nov.) 1941.

Hellebrandt and Karpovich made an exhaustive review of the literature on methods whereby output of work can be increased and fatigue lessened. The feeling of fatigue may be caused by an increase in magnitude of the work done, by heightened susceptibility to discomfort or by a combination of the two factors. The authors believe that the reasons for fatigue are more psychologic than physiologic.

The susceptibility to fatigue may be lessened by an improved state of nutrition and hygiene and heightened by the accumulation of metabolic wastes, depletion of fuel resources, disruption of the heat-regulating mechanism, circulatory collapse or lack of oxygen.

Measures used to combat fatigue (ergogenic measures) may act to delay the onset of exhaustion and hasten recuperation or to dull the awareness of fatigue. Measures with the first objective include those which augment the capacity to work by improving the condition of the machine (the safest and most physiologic approach).

A. Substances that promote gastric activity, such as (1) Bovril, which increases the acidity of the gastric juice and hastens the emptying time of the stomach; (2) powdered beef, which increases the pepsinogenizing activity of the gastric juices; (3) amphetamine, which increases both the hydrochloric acid and the pepsin content of the gastric juice, and (4) alcohol in small doses, which increases the hydrochloric acid but lowers the enzyme content of the gastric juice.

Exercise after eating does not decrease the digestive activity, but a full meal interferes with respiration, and this may lower the capacity for work. Emotional upsets tend to inhibit the digestive activity by reflex action.

B. Substances that supply added energy, such as (1) carbohydrates, which are the fuel of choice if the exertion is short lived and violent, and (2) fats, which are the fuel of choice if the exertion is prolonged and exhausting.

Lack of vitamins B, C and E decreases the capacity of the machine, but there is no evidence that an excess intake of these vitamins will increase the capacity.

Sodium chloride reduces muscular cramps in hot weather and so lessens fatigue. The best results are obtained by giving fluids containing the salt. Limitation of water intake results only in a concentration of the blood and so adds to fatigue.

The evidence for the value of alkalis is contradictory. Ammonium chloride apparently helps to counteract the alkalosis associated with subsistence at reduced oxygen pressures. Some observers disagree with this. Phosphates are supposed to cause a subjective feeling of freshness and zest, but reports are contradictory. Observations are also contradictory as to the beneficial effects of increased oxygen intake. It is well known, however, that a decreased oxygen intake limits the capacity for muscular exercise. Such a condition can be improved by the ingestion of carrots and, to a lesser degree, by eating parsnips, beets, apples and bananas. The evidence as to the value of endocrine medication is contradictory. For example, adrenal cortex extract increases the capacity for work in animals but apparently does not do so in man. Perhaps the apparent effect of endocrine substances is purely subjective in man.

Ingestion of gelatin has no effect in increasing the capacity for exertion.

Among measures which push the person beyond the normal limits of endurance, and are therefore potentially dangerous and should be reserved for use in emergencies, may be mentioned the use of (1) coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide), which removes fatigue by increasing the capacity of the heart (digitalis does not increase the capacity of the normal heart); (2) metrazol, which stimulates the vasomotor and respiratory centers and thus reduces fatigue and increases the ability for exertion, and (3) alcohol, caffeine, amphetamine and coca leaves, all of which raise the level of performance by lessening the appreciation of fatigue. Excitement energizes but may mar the actual performance. In fact, the performance of an excited person may be improved by the administration of sedatives.

The most enduring gain is obtained through systematic physical training associated with an increased desire to be fit.

PEARSON, Philadelphia.

THE RELATION BETWEEN THE ELECTROENCEPHALOGRAM AND FLYING ABILITY. MELVIN THORNER, FREDERIC GIBBS and ERNA L. GIBBS, War Med. **2**:255 (March) 1942.

Thorner, Gibbs and Gibbs correlated the electroencephalograms and the flying ability of 109 aviators. Men with spectrums of type B were better fliers than those with spectrums of type A. In type B the best fliers had the dominant peak at a frequency of 10½ per second. In type C, if the curve rose above 22 on the voltage side at any frequency greater than 24 per second there was a decrease in flying ability.

The best fliers were those with the following types of spectrums: type A, with the dominant peak centered at 10 or 10½ per second; type B, with the dominant peak centered at 10, 10½ or 11 per second, and type C, with the curve below 22 on the voltage side at frequencies of more than 24 per second.

An abnormal response to overventilation was associated with decreased flying ability. Three fliers with average or better than average flying ratings had epileptoid spectrums.

PEARSON, Philadelphia.

Psychiatry and Psychopathology

PSYCHONEUROTICS FIVE YEARS LATER. CONSTANCE FRIESS and MARJORY J. NELSON, Am. J. M. Sc. **203**:539 (April) 1942.

Friess and Nelson reviewed the records of 3,587 consecutive patients seen in a general medical clinic from Sept. 1, 1932 to Jan. 1, 1934. The diagnosis of psychoneurosis was made for 498 patients (13.9 per cent), and these were selected for the study. Patients who had received psychiatric treatment were reexamined by the psychiatrist, who was asked to compare the present psychiatric status with that five years previously. Of the 296 patients contacted, 109 (40.5 per cent) were males and 160 (59.5 per cent) females. Forty-five and three-tenths per cent of the group were less than 36 years of age. More than one-half the patients, 110, or 59 per cent, were married. The incidence of foreign-born patients was not as high (37 per cent) as it was in the general clinic (43 per cent). The proportion of Jews among patients with psychoneurotic disorders was greater than in the outpatient department—28 as compared with 16 per cent. Sixty-seven patients (25 per cent) had evidence of major organic disease and 150 patients (55.8 per cent) had evidence of minor organic disease at the time of their original visit. Only 48 patients (18 per cent) were cared for in one clinic, whereas 219 patients (81.4 per cent) attended five clinics or less and 50 patients (18.6 per cent) attended from six to twenty clinics. It was found that the referral of patients to more than five clinics was due rarely to diagnostic difficulties, but primarily to personality problems. One hundred and twenty-nine patients (48 per cent) received psychiatric treatment; 38 of these (14.1 per cent of the whole group) made more than five visits to a psychiatrist. There was no direct ratio between the severity of the neurosis and the amount of psychiatric treatment. In comparison of 179 psychoneurotic patients with 100 control patients, almost identical percentages of operative and nonoperative cases were found. However, the number of operations per patient in a group of neurotic patients was persistently higher than that in the control group (1.6 to 1.1), owing largely to the absence of cases of "surgical addiction" in the latter group.

Only 35 patients (13 per cent) had complaints related to one system of the body. By far the commonest complaints were those referred to the nervous system or to the body as a whole (154 patients, 57.2 per cent of the entire group). The second largest group, consisting of 111 patients (41.5 per cent), had complaints related to the gastrointestinal tract. Fifty-six patients had cardiovascular symptoms. Of the 61 patients with symptoms referable to the head, 55 complained of headache, two thirds of them being women. Symptoms referable to

the skeletal system occurred in 57 patients. Only 21 patients had genitourinary complaints. Respiratory symptoms were observed in 17 patients. All the 12 patients with symptoms of endocrine disturbance were women complaining of hot flushes associated with the menopause.

After a lapse of five years, two thirds of the patients questioned (116 patients) had the same complaints as at the original examination, thus indicating fixity of the complaint. For 8 per cent of patients the original diagnosis of psychoneurosis was incorrect. If the physician had been aware that positive evidence of neurotic personality traits and neurotic behavior is essential for a diagnosis, errors in this group could have been avoided. Eight patients (4 per cent) were considered free of symptoms, and 6 of these were gainfully employed. Forty-five patients (22.5 per cent) showed improvement, consisting of lessened intensity and frequency of symptoms. Eighty (40 per cent of the patients) interviewed gave no evidence of change in the psychiatric status. Thirty-six (18 per cent) showed progression of their neuroses. Of these, 9 required care in psychiatric institutions. Fifteen (7.5 per cent) had died. In no instance had death been due to an illness present but unrecognized at the time of the original diagnosis. In 19 patients organic disease was discovered at the time of the follow-up examination.

The cost of medical care during the period of study for the 269 psychoneurotic patients was $16,345, the average cost per patient being $60.76. For the psychoneurotic patient the cost of medical care is not proportionate to the clinical result. A higher proportion of psychoneurotic patients were cured or improved in the group attending five or less clinics than in the group attending six to twenty clinics. The authors make suggestions concerning the management of psychoneurotic patients in a general medical clinic. 1. Both functional and organic disease occurs in the same patient with great frequency. 2. The diagnosis of psychoneurosis should never be made solely on the basis of exclusion. 3. The type and extent of organic disease should be established early. 4. The type of psychotherapy which is indicated should be decided on early. This may help to prevent medical shopping. 5. The patient should have but one physician. The internist with adequate training, the proper attitude and a suitable clinic organization can, in a few concentrated interviews, make life more tolerable for many psychoneurotic patients, although he can cure relatively few. MICHAELS, Boston.

INSTINCT AND THE EGO DURING INFANCY. IVES HENDRICK, Psychoanalyt. Quart. **11**:33, 1942.

Hendrick discusses the part played by the instinct to mastery in the development of the child, together with its role in neurotic compulsion and the development of the ego. Infants under 2 years of age constantly learn to use their bodily tools for mastering the environment. In infants sexual fantasies and sexual play are common, as has been learned from direct observation and from reconstructions in the analyses of adults. The evidence from direct observation differs from that in reconstructions, since in the former the goal of the infantile erotism is not orgastic and the action itself is not compulsive; i. e., it does not culminate in orgastic satisfaction or in frustration with unrelieved tension and conflict unless there is associated anxiety. All these phenomena appear as part of the reconstructions in the analyses of adults, since, Hendrick believes, the memory has been energized by the sexual instinct after puberty; in other words, the infantile memories which occur in analysis should be regarded as the critical end points of the infantile memories which have been repressed.

Mature behavior is the synthesis of various partial abilities. Each of these shows three stages in development: 1. The emergence of physiologic ability to form a reflex pattern, for example, sucking reflex. 2. A period of practice and training; for example, the child's ability to suck increases as he practices sucking. 3. The mature proficiency in the use of the act.

The first phase is stereotyped and is more closely related to specific stimuli than to any useful objective or emotional need. In the second phase there is a

need to learn by repetition, which is independent of the specific stimuli and is followed by increasing ability to modify the stereotyped pattern. This learning process is the first objective appearance of the instinct to mastery and shows a compulsive need to practice the unlearned function. In the third phase there develops a proficiency in using the apparatus at will without further practice. The act is adapted to the use of the personality as a whole rather than as an exercise for its own sake. This adaptation is accompanied by an increasing degree of integration of all the partial functions. Later, compulsiveness consists of a regression to the normal stage of unlearned function and is associated with inability to exercise proficiently a function which gratifies the need to master. Undeveloped functions or those which are obstructed always provoke compulsiveness. This process of learning is the foundation of ego development. The more mature the ego the less evidence it shows of compulsive repetitiveness. This compulsive repetition is released (1) in the voluntary exercise of sensorimotor patterns before the capacity for efficient performance has been achieved by practice; (2) during the process of learning new patterns of a more complex nature prior to the attainment of efficient performance; (3) when the exercise of the mature function is disturbed by (*a*) external frustrations (by parents, the analytic transference neurosis and the limitations imposed by other persons or by a group), (*b*) anxiety and guilt, (*c*) realistic anxiety (real dangers, traumatic neuroses and panic) or (*d*) survival of a dominant compulsive pattern of instinct discharge which is not subordinated to reality principle or the superego (negative therapeutic reaction and the compulsive personality), and (4) when functions essential to normal adult object relations (psychoses, psychopathy, ego defect neuroses) have not matured.

PEARSON, Philadelphia.

DEMENTIA PRAECOX IN MILITARY LIFE AS COMPARED WITH DEMENTIA PRAECOX IN CIVIL LIFE. ADDISON M. DUVAL and J. L. HOFFMAN, War Med. **1**:854 (Nov.) 1941.

Of 5,000 patients with dementia praecox admitted to St. Elizabeths Hospital, about half were soldiers and half civilians. When these two groups were compared, it was found that the clinical picture presented by the soldiers was different from that presented by the civilians. In the former the onset was more abrupt, the course of the illness was more tempestuous, the situational factors were of more importance and more direct in their action and the prognosis, immediate and ultimate, was more favorable.

The types of soldiers in whom dementia praecox tended to develop were as follows: (1) men who up to the time of enlistment had led a sheltered life; (2) men whose fathers had died or had been absent during their childhood (these "mother's boys" tended to have cataleptic symptoms); (3) men with strong latent homosexual tendencies who tended to show acute homosexual panic; (4) men who were disillusioned and disappointed with military life and who tended to escape from it by catalepsy or suicide, and (5) men who entered the service because they felt inadequate and who tended to escape to grandiose delusions.

The diagnosis of many of the cases among soldiers was somewhat difficult. Of 100 soldiers suffering from dementia praecox, 47 were discharged from the hospital in less than a year; 40 of these 47 were discharged as improved or recovered.

PEARSON, Philadelphia.

TYPICAL POSTENCEPHALITIC PSYCHOSIS: REPORT OF A CASE. MARIO FUENTES, Arch. de neurol. y psyquiat. de Mexico **4**:21 (May-June) 1941.

Fuentes reports a detailed study of a patient with a typical postencephalitic psychosis occurring nine years after the onset of the initial infection. He describes "subcortical crises," which were precipitated by some emotional shock, and characterized by changes in respiration, cries of anguish and a generalized convulsion

without complete loss of consciousness. He ascribes this to a release of diencephalic function from cortical control. Further consideration is given to a sort of prehypnotic state with a content relative to the activities of the day in which the subconscious aspirations or tendencies are stressed. The pathogenesis is similar to ordinary dreams except that the conscious perception is stronger and there is a peculiar reality that dreams do not possess. The patient demonstrated an unusual, megalomanic attribute for transportation or projection of the body scheme into bizarre situations and places. The author calls this a type of "motor hallucination," or "motor paresthesia." Akin to this is a degree of dispersonalization or multiple personalization, differing from the same symptoms encountered in mania or hypomania, in which there are illusory disturbances, false perceptions and erroneous memories. This patient's discourse was coherent, and no affective changes were present. Ideational perception is described as a capacity for spontaneous variations in perception arising from a single stimulus, such as seeing a dog running on the ground and then the same dog running with his feet pointing upward. He considered this symptom a strong indication of postencephalitic psychosis not encountered in any other illness. MARSH, Los Angeles.

ASPECTS OF ALLERGY ASSOCIATED WITH NEUROSYPHILIS. EDUARDO BUENTELLO, Arch. de neurol. y psyquiat. de Mexico **4**:79 (July-Aug.) 1941.

Buentello proposes to answer several questions relative to the apparent discrepancy between the clinical symptoms and the serologic reactions encountered in cases of neurosyphilis. Statistics on the subject are cited from both the French and the German literature: Dujardin and Vermeylen reported 2 cases of typical dementia paralytica confirmed at autopsy but with negative serologic reactions. Ahronheim reported 443 cases of neurosyphilis, in 59 of which the serologic reactions of the spinal fluid were negative. Included in this group were 170 cases of tabes dorsalis, in 34 of which the fluid was normal, and 124 cases of meningomyelitis, in 25 of which the fluid was normal. The author adds 8 cases of neurosyphilis with typical clinical manifestations but with negative serologic reactions of the spinal fluid.

Emphasis is placed on various external factors capable of altering the serologic reactions without changing the course of the clinical symptoms. Specific medication of acute infectious diseases is able to modify and negativize the spinal fluid during the progress of the disease, but may not prevent the appearance of symptoms. The questions of the role of allergy and transient anallergic phases are discussed in the light of their relation to positive or negative serologic curves and certain forms of neurosyphilis. Tabes dorsalis and dementia paralytica are considered to be anallergic phases that may be converted to an allergic phase by malaria therapy. The cutaneous lesions of the secondary stage of syphilis constitute a good system of reticuloendothelial defense that seems to favor the development of allergy and impede the development of tabes or dementia paralytica. The author concludes that spontaneous immunization is the direct result of the cutaneous rash; therefore therapy should not be started until after the development of the rash. If this is slight or does not appear, actinotherapy or other irritative measures should be employed. MARSH, Los Angeles.

PSYCHIATRIC STUDIES ON A SERIES OF TWINS. ERIK ESSEN-MÖLLER, Acta psychiat. et neurol. (supp. 23) **8**:1, 1941.

Using Luxenburger's method of complete series, Essen-Möller examined 69 pairs of twins of the same sex among 10,000 patients in Swedish hospitals for mental disease. The author observed personally both twins of 41 pairs and one twin of 19 pairs. The question as to whether the twins were monozygotic or dizygotic was determined on the basis of physical resemblance, with the aid of descriptions, photographs and, if possible, examination. Twenty-one pairs were

monozygotic and 48 dizygotic. The monozygotic pairs are described and discussed in detail (a table with photographs is given) and questions of characterologic features and environmental and constitutional differences are dealt with in special chapters. The author gives a summary of his cases, which is translated verbatim as his classification and diagnostic conclusion are not identical with prevalent American views.

On the basis of this classification, the author finds a psychotic second twin in only 7 of his 21 monozygotic pairs, among whom were 1 with dementia paralytica,

Survey of Monozygotic Twins

	Twins	Patient's Psychosis	Twin: Psychosis	Twin: Characterologic Anomalies
1	Anton and Karl	Schizophrenia	Borderline	Present
2	Agnes and Berta	Schizophrenia	Reactive, with schizophrenic features	Present
3	Alfred and August	Schizophrenia	None	Present
4	Anselm and Konrad	Reactive psychosis and schizophrenia	Reactive state; induced	Present
5	Frida and Hanna	Schizophrenia	Depressive state; hallucinosis	Present
6	Julia and Ida	Schizophrenia	None	Present
7	Martha and Rosa	Schizophrenia with manic features	Depressions with schizophrenic symptoms	Present
8	Jenny and Klara	Nonsymptom states with excitement and anxiety; schizophrenic group	None	Absent (?)
9	Erika and Helena	Nonsymptom depressions, partly reactive; schizophrenic group	Psychosis with schizoid defects	Present
10	Rolf and Herbert	Reactive querulence with delusions of reference	None	Present
11	Hans and Rudolf	Senile schizophrenia	None	Present
12	Otto and Ragnar	Schizoid state after trauma	None	Present
13	Ernst and Holger	Cyclic phases of post-traumatic psychosis	None	Absent
14	Laura and Helga	Asthenic depression in hypertension	None	Present
15	Hilma and Blenda	Endocrine disturbance; reactive psychosis	None	Absent
16	Maria and Gerda	Endocrine disorder; reactive psychosis	None	Absent
17	Lina and Fanny	Manic-depressive and migrainous psychosis	Borderline	Absent (?)
18	Aina and Ester	Epilepsy with psychosis	None	Present
19	Selma and Astrid	Epilepsy with psychosis	None	Absent (?)
20	Alma and Tekla	Post-choreatic psychosis of exhaustion	None	Present (?)
21	Werner and Magnus	Dementia paralytica	None	Absent

1 with post-traumatic psychosis, 1 with postchoreatic psychosis, 2 with doubtful endocrine disorders and 1 with hypertension. In the first 10 pairs of psychotic twins one member was schizophrenic, and in at least 5 of these (pairs 1, 2, 5, 7 and 9), not in just 1 of 7 pairs, as the author states, the other twin was also schizophrenic.

The author points to the frequency and constancy of characterologic anomalies and psychopathic features of the twin in a large number of his original 21 pairs of psychotic twins. He believes that genetic studies prove that differentiation between psychotic and psychopathic, as well as schizophrenic and schizoid, is not important.

Only in the cases of Otto, Ernst, Alma and Werner does the author see clear environmental factors. In the other cases the influence of the environment was problematic. In 3 pairs there was no difference of environment, but the partners developed very differently. In 6 pairs characterologic differences developed before changes in the environment occurred. In many cases of hereditary "endogenous" psychoses it is likely, in view of quantitative expressions of characterologic anomalies, that environmental factors operate at very early stages in ontogenesis.

REDLICH, Boston.

Diseases of the Brain

A CLINICAL AND ANATOMICAL STUDY OF NEUROLOGICAL CONDITIONS RESULTING FROM METASTASES IN THE CENTRAL NERVOUS SYSTEM. A. B. KING and F. R. FORD, Bull. Johns Hopkins Hosp. **70**:124 (Feb.) 1942.

King and Ford noted 158 cases of carcinoma of the lung in a series of 27,000 autopsies, an incidence of slightly more than 0.5 per cent. In 100 of the 158 cases there had been a complete postmortem examination of the nervous system. In 27 of these 100 cases metastatic deposits were observed. A study was made of the cases to determine whether a correct diagnosis might have been made ante mortem. The following neurologic syndromes result from deposits in the nervous system: (*a*) a picture consistent with a single focal lesion of the brain (8 cases); (*b*) signs of multiple focal lesions in the brain (6 cases); (*c*) a presenting symptom of stupor without definite focal signs (6 cases); (*d*) multiple lesions in the brain and spinal cord (1 case), and (*e*) involvement of the spinal cord alone.

Analysis of the individual symptoms and signs led to the following conclusions: 1. Focal signs are usually mild and incomplete. They are frequently of rapid onset and development and occur so abruptly as to suggest embolism, thrombosis or hemorrhage. 2. Not infrequently convulsions mark the onset of nervous symptoms, and these are frequently followed by hemiplegia. 3. Headache is frequent, but papilledema was present in only 5 of 27 cases. 4. The signs of meningeal irritation are rare. 5. Mental disturbances are common but not characteristic. Drowsiness, passing into stupor and coma, is most frequently observed. Delirium and excitement are rare.

In 3 of 10 cases examined the spinal fluid pressure was increased. There was usually an excess of protein in the spinal fluid. In cases in which there were neurologic signs roentgenograms of the skull and bones rarely revealed metastases. The growth in the lungs might be silent at a time when the neurologic symptoms were well advanced.

It is suggested that in all cases in which there is reason to suspect an intracranial neoplasm or a neoplasm of the spinal cord or there is unexplained stupor a careful roentgenographic examination be made of the chest for neoplasm of the lung.

PRICE, Philadelphia.

ELECTROENCEPHALOGRAPHY IN CASES OF HEAD INJURY. J. MARMOR and N. SAVITSKY, J. Nerv. & Ment. Dis. **95**:285 (March) 1942.

Marmor and Savitsky in this study attempt to achieve further objective criteria for the presence or absence of organic changes in post-traumatic syndromes. Twenty-eight patients with various types of head injury, falling into four main groups, were examined electroencephalographically. Group 1: Postconcussion syndrome. Eight of the 11 patients showed various electroencephalographic abnormalities, varying from a poor alpha rhythm to a completely disorganized irregular rhythm of variable frequency. Group 2: Postconcussion syndrome with psychogenic superimposition. The 8 patients showed, in addition to the postconcussion syndrome, such manifestations as traumatic hysteria and terror neuroses. Four had abnormal and the remaining 4 normal electroencephalograms. Group 3: Post-

traumatic epilepsy. All 5 patients had abnormal electroencephalograms, characterized by poor alpha activity and occasional spontaneous bursts of slow potentials of high amplitude. Group 4: Traumatic hysteria. The 4 patients in this group, all presenting only conversion phenomena, had entirely normal electroencephalograms.

The authors believe that their observations indicate the probable organic character of the postconcussion syndrome. The abnormal rhythm observed after head injuries in most cases tends to subside after a few months; hence a normal electroencephalogram does not rule out postconcussion syndrome.

CHODOFF, Washington, D. C.

THE OCCURRENCE OF UNILATERAL (JACKSONIAN) GRAND MAL SEIZURES IN TETANY. J. M. MEREDITH, J. Nerv. & Ment. Dis. **95**:405 (April) 1942.

Meredith states that only 3 instances of unilateral convulsions due to tetany have been recorded. He reports the case of a 3 year old Negro boy who had severe clonic convulsive seizures on the right side, with complete loss of consciousness. Studies of the calcium and phosphorus of the blood and the presence of Erb's sign established the diagnosis of tetany and rickets, and there was prompt improvement after treatment with calcium gluconate and viosterol. Follow-up studies showed no recurrence, although a suggestive Erb sign forty-nine months later indicated subclinical tetany.

The early clinical picture was similar to that seen with a mass intracerebral lesion, and it is suggested that tetany be considered in the differential diagnosis of similar conditions. The author believes that a reading of less than + 5 milliamperes in the cathodal closing contraction with the galvanic current in a child under 5 years of age is suggestive of low diffusible calcium in the tissues and establishes the diagnosis of tetany. He emphasizes the fact that Erb's phenomenon is the most persistent and reliable sign of spasmophilia and the last to disappear. Certain cases of so-called idiopathic epilepsy in children may actually be instances of tetany with an average blood calcium but a lowered tissue (ionized) calcium content.

CHODOFF, Washington, D. C.

SOME REMARKS ON TUMORS OF THE BRAIN IN CHILDHOOD. OTTO MARBURG, J. Nerv. & Ment. Dis. **95**:446 (April) 1942.

From a review of the statistics of various authors, Marburg concludes that 14 to 15 per cent of all tumors of the brain occur in childhood. There is an increase in the number of cases from the first to the sixth year and a drop at the seventh year, this level being approximately maintained thereafter. Fifty to 60 per cent of the tumors are subtentorial, and about 30 per cent occur in the diencephalic region. Some cerebellar cysts and cystic astrocytomas are dysraphic, depending on disturbance of the closure lines of the neural tube. Others, such as tumors of the craniopharyngeal duct, cysts of Rathke's pouch, and pineal and infundibular neoplasms, may be considered as diverticular tumors. A third group comprises the tumors of transformation, such as those originating in the posterior velum.

Tumors of the hypophysis and the pineal gland are characterized principally by growth disturbances of various types. The existence of acromegaly in childhood has not been proved conclusively, although the transitory acromegaly of adolescence is recognized. Pubertas praecox occurs only in persons with complete destruction of the pineal gland before the age of 7. With destruction developing later, there occurs premature development of secondary sex characters. Tumors of the quadrigeminal plate may cause Nothnagel's syndrome—bilateral incomplete oculomotor palsy followed by ataxia. Tumors within the third ventricle cause symptoms similar to those of hypophysial and pineal tumors and are difficult to diagnose, although ventriculography may help.

Ataxia is a frequent and important symptom of tumor of the brain in childhood and may occur in cases of supratentorial or subtentorial growths. It may be cerebellovestibular, due either to hydrocephalus, with pressure on the cerebellum, or to choked labyrinth, but clinically there also occur frontal and temporal ataxias. Frontal ataxia is less severe; the deviation is contralateral, and vestibular signs are present only occasionally. Temporal ataxia resembles the frontal variety, but with more severe vestibular involvement, possibly because the temporal lobe is the cortical center for vestibular function.

Convulsions are common with the tumors of childhood and are more undifferentiated than those seen in adults. Their frequency depends on the accompanying hydrocephalus and to a lesser degree, on the site and nature of the tumor, blood vessel growths being particularly likely to cause epilepsy.

As to the type of tumors occurring in childhood, the views of Cushing and his group are accepted. The relative frequency of tumors of the glioma group is due to the immaturity of the cell types of which these tumors are composed and their consequent faster development and earlier appearance. The malignant nature of these neoplasms invalidates neurosurgical skill, except for the astrocytomas and some cystic tumors.

CHODOFF, Washington, D. C.

CALCIFIED EPENDYMOBLASTOMA OF THE FOURTH VENTRICLE IN A FOUR-YEAR-OLD GIRL. EDWIN BOLDREY and EARL R. MILLER, Radiology **38**:495 (April) 1942.

Calcification of gliomas is rarely observed in children under 4 years of age, and more rarely still is it capable of roentgenographic demonstration, particularly if the tumor is located in the posterior fossa. The authors report the case of a child aged 3 years 7 months who had a calcified ependymoblastoma of the fourth ventricle.

In an analysis of 100 intracranial tumors in children, Bailey, Buchanan and Bucy found 7 ependymomas, 5 of which occurred before the age of 4 years. The greater proportion of such tumors occurred in males. Only 1 of these was reported as showing calcification, and this was seen only on microscopic study.

The case which the authors report is unique, since the growth of the tumor, its degeneration and replacement by colloid, with subsequent calcification, required considerable time. No other instance of calcification in an ependymoma in a patient under 4 years of age has been discovered.

KENNEDY, Philadelphia.

VISUAL FIELD CHANGES AND SUBDURAL HEMATOMAS. GEORGE L. MALTBY, Surg., Gynec. & Obst. **74**:496 (Feb.) 1942.

Of a series of 62 cases of verified subdural hematoma, visual field defects were found in 7. In all instances the defect was homonymous, and in 4 it was contralateral to the hematoma. Abnormalities were observed postoperatively in 4 cases. In 2 cases in which field defects were present and operation was performed the patients died. In both cases there was herniation of the uncal portion of the hippocampal gyrus, with indication of interference with the posterior cerebral artery. The tentorial pressure cone was responsible for the false localizing signs, but the embarrassment of circulation in the posterior cerebral artery from a herniated hippocampal uncus may have caused some of the residual visual field defects.

GOTTEN, Memphis, Tenn.

INTRACRANIAL INFECTIONS AND THEIR SPREAD FROM THE EAR AND THE NASAL ACCESSORY SINUSES. A. C. FURSTENBERG, Surg., Gynec. & Obst. **74**:585 (Feb.) 1942.

The usual course of an inflammatory process in the temporal bone that gives rise to an intracranial complication is one which causes destruction of tissue by continuity of infection and ultimately reaches the subarachnoid space by direct extension through the dura mater. Exceptions result from hematogenous dis-

semination of infection. Infection acquired while swimming is a common cause of acute sinusitis with intracranial complications, the mechanism probably being thrombosis of the veins of the mucous membrane of the frontal sinuses which communicate with the dense plexus of veins in the coverings of the brain.

Operation should be avoided in the presence of a "green" infection, as this may predispose to osteomyelitis of the skull. Drainage of soft tissues is the method of choice, removal of bone being left for the chronic conditions only. In most cases of acute sinusitis in swimmers the meningeal infection, if present, occurs at about the same time. The method of spread of abscess to the brain is by perivascular infiltration, not by migration of septic thrombi within the pial and cerebral veins.

GOTTEN, Memphis, Tenn.

THE PATHOGENESIS OF TRAUMATIC UNCONCIOUSNESS. W. DE GUTIÉRREZ-MAHONEY, War Med. **1**:816 (Nov.) 1941.

De Gutiérrez-Mahoney studied the brains of 4 patients who died within forty-eight hours after injury to the head and the brains of dogs who had been exposed experimentally to cerebral injury to determine the cause of concussion, i. e., to explain the possibility of total paralysis of cerebral function followed by complete recovery. In three types of experiments on the dogs, force was applied (1) to the fixed head, (2) to the unfixed head and (3) to the exposed brain.

In the human brains round structureless areas were scattered through the white matter. The small blood vessels were dilated and surrounded by red cells. The cell bodies of the neurons were disrupted, and the Nissl architecture was disorganized, with many vacuolations, which were filled with fat. The white matter showed demyelination and collections of fat about the vessels.

The brains of the dogs with the first type of injury showed no histologic changes, while those of dogs with the second and third types of injury had the same changes observed in the human brain.

The author believes that unconsciousness which follows head injury is the result of elimination of many brain elements. Because of the nature of the skull, the trauma is transmitted to all centers. It liberates fat, thus producing fat emboli which plug the cerebral vessels and cause nutritional deficiency. Since the arteries of the brain are not end arteries and the fat particles have ameboid activities, the arteries are plugged only temporarily. The liberated fat elements also have parasympathetic-like effects and are partly responsible for the shock which follows injury to the head.

PEARSON, Philadelphia.

ANALYSIS OF THREE HUNDRED AND SEVENTY-THREE CASES OF ACUTE CRANIOCEREBRAL INJURY. COBB PILCHER and RALPH ANGELUCCI, War Med. **2**: 114 (Jan.) 1942.

Pilcher and Angelucci report an analysis of the clinical symptoms of 373 patients with acute head injury. The injuries of 49.1 per cent were classified as mild or moderate and those of 24.1 per cent as severe. Thirteen and nine-tenths per cent died. Twenty-three patients over 60 but only 5.7 per cent under 10 years of age died. The most important prognostic factor was the degree of unconsciousness. The authors believe that the prognosis is bad if there are marked pupillary changes, severe paralysis, convulsions, a temperature over 103 F. and irregular or labored respiration. This type of respiration was present in 80.8 per cent of the patients who died, in contrast to an incidence of only 27.6 per cent for the entire group. Serious prognostic signs are a low systolic pressure, pronounced elevation or decrease in the pulse pressure and a compound fracture involving the dura. Signs which formerly were regarded as signifying a bad prognosis, i. e., a rise in systolic blood pressure and slow pulse and respiratory rates, were found to be of little importance in this series.

The number of the whole group who died was 35.8 per cent. Of these, 40.3 per cent died within the first twelve hours. In the second twelve hours only

21.2 per cent died. Eighty-one and seven-tenths per cent were discharged from the hospital free of neurologic signs. In the whole series the outcome was influenced by therapy in only 5.4 per cent.

PEARSON, Philadelphia.

Treatment, Neurosurgery

ELECTRIC CONVULSION THERAPY IN PSYCHOSES. DOUGLAS GOLDMAN and E. A. BABER, Am. J. M. Sc. **203**:354 (March) 1942.

Goldman and Baber completed electric shock treatment of 68 patients, 49 with schizophrenia, 13 with manic-depressive and involutional psychoses and 6 with other forms of psychosis. The treatment was given with the patient in bed and a pillow under the dorsal region of the spine to hyperextend the vertebral column. The initial dose was 450 milliamperes applied for three-tenths second, since almost all patients have seizures with this dose. A 60 cycle alternating current was used. The duration of the seizure varied from thirty to ninety seconds and was usually less than that of the metrazol seizure. Patients awakened more rapidly and with less confusion as a rule after electric shock than after metrazol seizures. There was complete amnesia for the period of treatment and for a short time before and after. The complications encountered were dislocation of the jaw and, in 1 case, fracture of the head of the humerus. The outstanding feature was the total absence of fear of the treatment on the part of patients who had had one or more treatments. The results of electric convulsion therapy hardly differed from those observed after metrazol shock treatment. The results were favorable in inverse proportion to the duration of illness. A duration of any psychosis for more than one year is likely to indicate an unfavorable prognosis. Of the 68 patients treated, 9 were regarded as recovered, 13 had a "social remission," 33 more were regarded as improved and 13 were unimproved.

MICHAELS, Boston.

THE ROLE OF ABSTINENCE IN THE ETIOLOGY OF DELIRIUM TREMENS. J. G. SHEPS, J. Nerv. & Ment. Dis. **95**:278 (March) 1942.

Sheps attempts to answer the question whether or not the giving of alcohol is ever necessary to avoid a full blown attack of delirium tremens. From a review of the literature he concludes that clinical evidence supports the contention that, provided the general needs of the patient are met, the administration of alcohol has no place in the treatment of this phase of alcoholism. The author studied 104 patients, all with chronic alcoholism, who had been drinking up to admission and who were restless and complaining of nervousness and sleeplessness. All received hydrotherapy, sedation as necessary and a diet adequate in calories, and in no instance did delirium tremens develop. The observations of various workers indicate the constant occurrence of damage to the liver in alcoholism. This is a further contraindication to the use of alcohol in treatment of this condition.

CHODOFF, Washington, D. C.

METRAZOL THERAPY IN THE AFFECTIVE PSYCHOSES. EUGENE ZISKIND, ESTHER SOMERFELD-ZISKIND and LOUIS ZISKIND, J. Nerv. & Ment. Dis. **95**:460 (April) 1942.

Ziskind, Somerfeld-Ziskind and Ziskind analyze the results of treatment with metrazol in a controlled group of cases of the affective psychoses in order to determine whether the therapeutic results exceed the spontaneous cures and to compare the complications of the therapy with those of the untreated illness. There were 38 treated and 45 untreated patients, with 92 per cent of complete and partial remissions among the former and 72 per cent among the latter. The latter figure would be 53 per cent if only the untreated patients were considered for whom treatment was recommended but refused. The average duration of illness was

one and a half months for the treated patients, as against six months for the untreated ones. Among the untreated patients there were 5 deaths, 2 from exhaustion and 3 from suicide, while 1 treated patient committed suicide. Relapses occurred primarily in patients receiving inadequate therapy and did not appear in fully treated patients. In those patients in whom the injections produced a substantial number of subconvulsive reactions, there were full remissions in only 43 per cent, while 100 per cent of those with satisfactory convulsions at every injection recovered. The reactions were similar in patients with manic and in those with depressed states. The authors believe that these figures prove the beneficial effect of metrazol on the affective psychoses.

Clinical fractures occurred in 6 and subclinical fractures in 31 per cent of treated patients. The latter are not considered serious or a deterrent to treatment. The authors believe that the incidence of clinical fractures is more than balanced by the increased death rate of the untreated patients. The problem of irreversible damage to the brain from the use of metrazol is still *sub judice,* and evidence is not yet sufficient to contraindicate the use of the method.

Improvement is probably on a physicochemical basis, and the theory of a psychologic change is considered to be unwarranted by the evidence. Each case in which there was a physical condition possibly contraindicating treatment must be considered separately. Treatments should not be given more frequently than two or three times a week.

CHODOFF, Washington, D. C.

THE TREATMENT OF "METRAZOL FAILURES" WITH INSULIN. JACK WEINBERG and H. H. GOLDSTEIN, J. Nerv. & Ment. Dis. **95**:597 (May) 1942.

Weinberg and Goldstein report the results obtained in a series of 100 patients treated with insulin therapy after they had failed to respond to metrazol treatment. The patients were all women and consisted of 85 with schizophrenia, 11 with manic-depressive psychosis, 1 with involutional melancholia and 1 with psychoneurosis. Two were unclassified. All had failed to respond to metrazol, and after a rest period of three months were subjected to the Sakel technic for from six weeks to three months. There were 16 recoveries, 16 social recoveries and 37 institutional improvements. Thirty failed to show any improvement. Good results were much more frequent in patients treated within eighteen months of the onset of their psychosis. Of the types of disorders treated, catatonic excitements and manic phases of manic-depressive psychoses made the most favorable response, while depressions and hebephrenic dementia praecox did not improve as much. Thirty-six patients were discharged from the hospital, but 5 had a relapse and were readmitted.

CHODOFF, Langley Field, Va.

TREATMENT OF EQUINE ENCEPHALOMYELITIS (WESTERN) WITH CERTAIN SULFONAMIDE COMPOUNDS. C. F. SCHLOTTHAUER, Proc. Staff Meet., Mayo Clin. **17**:187 (March 25) 1942.

Schlotthauer inoculated guinea pigs by intracranial injection of 0.2 cc. of a 30 per cent emulsion of brain infected with the virus of western equine encephalomyelitis. Fatal encephalitis was produced in 100 per cent of the animals, with death in three to seven days. Inoculation of 0.2 cc. of a similar brain emulsion into the pad of the left hindfoot of susceptible guinea pigs caused fatal encephalitis in only 72 per cent. Similar inoculations intracranially and into the foot pad of vaccinated guinea pigs produced no apparent ill effects.

The virus of the western strain of equine encephalomyelitis was inoculated intracranially in one series of guinea pigs and into the foot pad in another series. The animals were then treated with sulfanilamide, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole), sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine), promin (sodium p,p′-diaminodiphenylsulfone-n,n′-didextrose sulfonate) and eight other compounds of sulfanilamide. None of the drugs used appeared

to have specific inhibiting effects on the virus of the western strain of equine encephalomyelitis. The disease ran a similar course in both treated and untreated animals. All the treated and untreated animals receiving the virus intracranially died, and 91 per cent of the treated and 75 per cent of the untreated guinea pigs receiving the virus in the pad of the hindfoot died.

ALPERS, Philadelphia.

POTASSIUM THIOCYANATE IN THE TREATMENT OF MIGRAINE. A PRELIMINARY REPORT. E. A. HINES JR. and L. M. EATON, Proc. Staff Meet., Mayo Clin. **17**:254 (April 22) 1942.

Migraine or a history of migraine was found in a previous study in 80 per cent of a group of patients suffering from essential hypertension and in only 15 per cent of a control group. Treatment of a group of such patients with potassium thiocyanate resulted in relief of the migraine in some cases. Of 100 consecutive patients who received this treatment for hypertension, 51 had migraine as a prominent complaint. Of these, 32, or 62.7 per cent, were entirely relieved of their attacks of migraine for from three to twenty-seven months, and 10, or 19.6 per cent, obtained partial relief.

Because of these experiences, potassium thiocyanate has been tried for patients with migraine, especially those with frequent and severe attacks and those not benefited by previous means of treatment. Fifteen patients have been treated for three months or longer. Of 13 patients with satisfactory blood thiocyanate levels (6 to 12 mg.), all received some definite relief. In the majority the frequence of headaches was reduced by 75 per cent, the average number of headaches for the three month period before treatment being 14, as compared with an average of 3.1 attacks after treatment was begun. It was found in 4 patients that the headaches increased in frequency when the level of thiocyanate in the blood fell to 1 mg. and decreased again when it rose to 10 to 12 mg., which was found to be the optimum level.

In none of the patients did toxic manifestations develop. These are not likely to occur if the thiocyanate level in the blood is less than 15 mg. per hundred cubic millimeters. The authors urge that the drug be used only under properly controlled conditions because of its potentially serious toxic effects.

ALPERS, Philadelphia.

THE SCALENUS ANTICUS FACTOR IN CONGENITAL TORTICOLLIS. SIDNEY M. COPELAND, Surgery **11**:624, 1942.

Copeland reports 3 cases in which resistance to overcorrection of torticollis was noted at operation after the appropriate sternocleidomastoid muscle had been cut. In each case hypertrophy of the scalenus anticus muscle was the obstructing factor, and severance of this additional muscle was followed by an excellent result in all 3 cases. Injury at birth was thought to have been the significant etiologic factor in these cases. The scalenus muscle may have become short secondary to injury and fibrosis of the overlying sternocleidomastoid, or it may have suffered primary injury itself. Exploration of the scalenus anticus muscle is recommended during all operations for torticollis.

DRAYER, Philadelphia.

SURGICAL TREATMENT OF SPASMODIC FACIAL TIC. WILLIAM J. GERMAN, Surgery **11**:912, 1942.

German reports 4 cases in which partial section of primary branches of the facial nerve gave relief from a facial tic, with little or no paralysis. After exposure of the nerve at operation, the branches which supplied the muscles involved in the tic were identified by electrical stimulation. A small flap was turned back on each such branch. These flaps were about three-quarters as thick as the branch on which they were made. They were doubled back proximally and held in place by a loose suture.

DRAYER, Philadelphia.

Diseases of Skull and Vertebrae

FRACTURES OF VERTEBRAL PROCESSES. R. K. GHORMLEY and H. O. E. HOFFMANN, Proc. Staff Meet., Mayo Clin. **17**:17 (Jan. 14) 1942.

Ghormley and Hoffmann review 823 cases of vertebral fractures of all types. Of these, 51 were instances of fractures of vertebral bodies with dislocation. In 90 of the 772 cases in which dislocation had not occurred lesions of the neural arch and processes were present. The cervical vertebrae were involved in 33 cases, the thoracic in 4 cases and the lumbar in 53 cases. Forty lesions were found in the cervical vertebrae, 5 in the thoracic and 106 in the lumbar, a total of 151 lesions.

ALPERS, Philadelphia.

HYPEROSTOSIS FRONTALIS INTERNA: ITS RELATIONSHIP TO CEREBRAL ATROPHY. R. M. STEWART, J. Ment. Sc. **87**:601 (Oct.) 1941.

Stewart discusses the possible relation between cortical atrophy and osseous change. He states, "Three alternatives may be entertained: (1) Brain atrophy is caused by the encroachment and pressure of the hyperostotic area on the surface of the brain; (2) brain atrophy is primary, the shrinkage of the frontal convolutions in some way exciting a compensatory bony overgrowth; (3) the two processes, osseous and neural, are entirely independent of each other."

There is little evidence in favor of the first view; the process of bony accretion is slow, and the degree of cortical atrophy is never striking and never in proportion to the amount of hyperostosis present. The second possibility is dismissed by virtue of the case reported by Stewart, in which the thickening of the pars frontalis in a case of advanced hyperostosis frontalis interna was unequal, the osteophytic growth being much more evident on the left side than on the right. On the other hand, the brain showed massive lobar softening, of three years' duration, limited to the right cerebral hemisphere, the other hemisphere having only a minor degree of senile atrophy. Stewart concludes that this crossed relation between the gross atrophy of the right cerebral hemisphere and the thicker left half of the pars frontalis lends no support to the view that in hyperostosis frontalis interna reduction of the volume of the brain stimulates the deposit of new bone on the inner table of the frontal bone.

BRACELAND, Chicago.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

ROY R. GRINKER, M.D., *President, in the Chair*

Regular Meeting, Feb. 19, 1942

A New Tendon Stretch Reflex: Its Significance in Lesions of the Pyramidal Tracts. DR. VICTOR E. GONDA.

This paper was published, with discussion, in the October issue of the ARCHIVES, page 531.

Acute and Subacute Toxic Myelopathies Following Therapy with the Arsphenamines. DR. BEN W. LICHTENSTEIN.

This paper, with discussion, appears in this issue of the ARCHIVES, page 740.

Congenital Atresia of the Foramens of Luschka and Magendie. DR. JOHN A. TAGGART and DR. A. EARL WALKER.

This paper was published, with discussion, in the October issue of the ARCHIVES, page 583.

PHILADELPHIA PSYCHIATRIC SOCIETY

ARTHUR P. NOYES, M.D., *President, in the Chair*

Regular Meeting, March 13, 1942

Psychiatry and Education. DR. FRANCIS J. O'BRIEN, New York.

The philosophy of modern education may be stated in several ways. These various definitions, however, indicate a single purpose, namely, the wholesome development of the total personality of the individual child. This philosophy of modern education recognizes in practice, as well as in theory, that each child is different from every other child; that the intellectual, emotional, physical, moral and social assets and deficiencies of each child must be known if adequate provision is to be made for an educational program suited to his varying needs and abilities.

As modern education, therefore, accepts the responsibility for the healthy development of the complete child, it has become primarily a clinical profession, of which the teaching of academic subjects is only one, and not necessarily the most important, aspect. It is evident, then, that the preparation teachers formerly received is not sufficient to enable them to determine these varying needs and to provide the different types of help needed by children.

Psychologic methods of testing have been developed along scientific lines, and these results are of inestimable value to the teacher. Home conditions, especially the interplay of personalities within the family group; physical health, and economic, social and racial forces frequently influence the child's attitude toward his school experiences and condition, to a large extent, his social and academic success or failure. Therefore the contributions of the psychiatrist, the pediatrician

and the psychiatric social worker are needed if the teacher is to be aided in understanding how these various influences are affecting the conduct of individual children. For these reasons, the psychologist, the psychiatric social worker, the pediatrician and the psychiatrist, in addition to the social case worker, the recreational worker, the clergy, the parents and the classroom teacher constitute the "team" that is necessary to discharge the duties and responsibilities assumed by modern education.

Formerly, little systematic attention was given to the role of causes in behavior, except in terms of physical illness. For example, whereas the "disciplinary" approach to undesirable behavior might be satisfying to the adult because the controls were projected on the symptoms (behavior), and not on the causes, the results were not only temporary but frequently injurious to the child's mental health. Clinical case records clearly demonstrate the necessity of understanding the causes of behavior, including, among other factors, the nature of and the important role played by the emotions, the role of the unconscious, the nature and significance of mental mechanisms and the need for cooperation with other professions if the complete child is to be understood as a prerequisite for the healthy modification or improvement of his behavior.

In the field of social psychiatry or mental hygiene many leading educators believed that they had found some of the knowledge and skills that modern education needed to discharge its newly accepted responsibilities. The child guidance clinic had brought together the pediatrician, the clinical psychologist, the psychiatric social worker and the psychiatrist, to work as "a team." In addition, the child guidance personnel are interested in the complete child, in discovering causes, in providing individual help and in improving methods both of diagnosis and of treatment. This approach to the understanding of the total behavior of children was recognized as practically identical with those needed in modern education.

As a result, several school systems during recent years have developed bureaus of child guidance as an integral part of their organization. In some cities educational systems make use of child guidance services that are provided by other community agencies.

In view of the broadened scope of modern education, it is evident that present day psychiatry has a contribution to make. However, if the psychiatrist is to be able to participate in the field of education, he must be especially prepared for it. His professional preparation must include adequate training and experience in dealing with the problems of adult psychiatry, as well as special training and experience in child psychiatry. In addition, he must possess certain personality characteristics, such as a liking for children, ability to work with persons in other professions, desire and ability to learn from them, an eclectic attitude in his own professional approach, teaching and supervising abilities, tolerance and a desire to benefit from and to integrate into his program the contribution of parents, teachers, clergy, social, health and recreational workers and any others who in any way may be able to contribute to the complete understanding of and the total educational program needed by each child. He must recognize particularly that he has at least as much to learn from educators as he has to give them.

DISCUSSION

DR. HAROLD D. PALMER: I shall speak briefly about the responsibilities of psychiatrists in the college or the university. A college mental hygiene program should consider as its most important problem the early detection of and contact with the unstable student. The second function of the college psychiatrist is the spreading of mental hygiene propaganda for the student and for the faculty, which function Dr. O'Brien describes as the educational. The third function is the treatment required in the student health service, where the psychiatrist is in association with other physicians on the student health staff. The fourth function is to act as a liaison officer between faculty and student by way of the personnel officers and the deans.

In regard to the first function, my associates and I have tried several methods at the University of Pennsylvania over a period of ten years; the present plan is not an ideal one, but works remarkably well. On admission every freshman fills out a detailed questionnaire called "Physical Examination Form of the Student Health Service." Emphasis throughout is placed on problems and disorders characteristic of college students, and the questions are so designed as to bring out a remarkably thorough psychiatric history. By a study of the information furnished by this questionnaire it is possible to obtain a family history, a past medical history, some idea of the circumstances under which the student lives, how he uses his spare time and the regularity and correctness of his dietary and sleep habits. In addition to questions about various somatic symptoms and the student's own evaluation of his state of health, there is a direct question inquiring whether he wishes to discuss any personal problem with the physician. The questions are so distributed that the student is not aware that he is giving any personal psychiatric data. The psychiatrist may review this questionnaire in a minute or two and get a fair picture of the nervous and mental integrity of the student. This is reviewed at the time of the entrance physical examination, and every student is interviewed personally by a psychiatrist. All students whose questionnaires are heavily weighted with answers indicating neuroticism are classified under a letter indicating need for immediate psychiatric interview. We have found the responses of the students gratifying, and most of them welcome the opportunity for discussion of their personal problems. It is found that 16.8 per cent of students have acute emotional disturbances of such proportion as to warrant psychotherapy. In the past three years about 800 students have been followed therapeutically in the mental hygiene clinic of the university.

As for the propagandist, or educational, function of the psychiatrist, the first need is to reach the student directly as soon as possible after his entrance into the school. Each year a series of four lectures is given to the freshman students in the Wharton School; these cover the mental hygiene needs of college students and the value of balanced college life, and the students are advised that there is a mental hygiene division which is eager to assist them in their personal difficulties. The college psychiatrist also takes part in a course given in the college for women on "Preparation for Marriage." In addition, a course of thirty-three hours covering the field of mental hygiene, particularly in relation to adolescent children, is given in the department of education. Dr. Harry Lees, the director of the student health service, discovered recently that while 56 per cent of the students in the required general hygiene course had received instruction in sewage disposal, only 13.1 per cent had received any instruction whatever in subjects relating to mental hygiene. The students thought that the instructors purposely avoided anything bordering on the subject of sex hygiene and that no time was allowed for personal interviews. Dr. Lees proceeded from that point to discover that 40 per cent of the freshmen students had sought advice from persons other than physicians for sexual and emotional problems. One hundred per cent felt that an opportunity should be given the student with personal difficulties to discuss them with a psychiatrist. It is obvious that the spreading of mental hygiene propaganda among the faculty is also an important function of the college psychiatrist. The service should be expanded to offer personal assistance to faculty members who indicate a need for psychiatric guidance. In our experience, faculty members in general are most responsive to our mental hygiene efforts and cooperate by personally assisting in many of the problems of maladjustment among the students.

In regard to the follow-up interviews and active therapy, I am sure every college psychiatrist would support our optimistic feeling that the students are remarkably responsive to a minimum of therapeutic effort. The ease with which maladjustments are straightened out and the apparent lasting benefit of the treatment are astonishing and indicate the phenomenal flexibility, resourcefulness and resilience of the college student.

The fourth, or liaison, function of the psychiatrist proceeds almost automatically by reason of the discussion of the specific case situations with the deans and personnel officers. The college psychiatrist brings an entirely objective attitude to the case discussions, and the usual outcome of the conferences with deans, personnel officers, professors and instructors is that all concerned derive a feeling of having helped the student rather than of functioning only as disciplinary agents. In connection with college disciplinary action, I must point out that one of the pitfalls in college work is the danger of becoming the "college executioner." It is easy and convenient for the deans to utilize the opinion of the college psychiatrist as the reason for dismissal from college. It can be quickly known on the campus that one's being referred to the college psychiatrist is followed all too soon by dismissal from school on the basis of nervous and mental instability. We have been on guard against this during our twelve years at the university and have had excellent cooperation from all the departments.

The nature of the emotional instabilities of college students is not radically different from the maladjustments encountered in psychiatric practice, but the student is somewhat more impatient, and he is usually seen in a more acute, and prognostically more favorable, stage of neurotic development. Many students, meagerly equipped with personal background, personality attributes and character, carry into their college life the hazards of warped personalities and emotional tensions. Many are pursued by unfavorable family influences even throughout their college years. In every instance of serious, crippling personality defects that we have studied, the roots of the problem have been found to reach back into the home soil. The duty of the college psychiatrist, and of others who make up the mental hygiene support of any institution, is not only to maintain some degree of equilibrium but to bring about greater stability and healthy growth of the personality in the unstable boy or girl during the precarious years of college life.

Dr. Earl D. Bond: I wonder how many educators would say that the public school should take care of the education of the total personality, and whether the public would see it that way, especially in Philadelphia and New York. For that reason, it is too bad that Dr. Gerson is not here tonight to speak for this locality. Dr. O'Brien said that modern education is a clinical function; I wonder whether it would not be better to say that future education ought to be a clinical function. Suppose the school tries to educate the personality, and not to keep to the books and the laboratory? I wonder whether there would not be considerable opposition.

I know of a boy who did build character on the school. He had been a little Lord Fauntleroy, brought to school by his mother or his nurse. He was not permitted to do even one little thing in the gymnasium for fear he would get a splinter which would become infected and lead to trouble. At the age of 8½ he was placed in a private school. He had a tough time for the first year and was often brought home tattered and torn. Finally, one of the men teachers saw that the boy did not know how to hit. He took him off in a corner and showed him how. The boy gradually improved in school and found himself in college. He has had no trouble, and he now looks back on his school as the place that saved him. He is very loyal. He built his personality on the school. He hates his father and mother; his chief wish is that he may never see either of them again. In school, a child may get the idea that there is something better than home. I agree that the psychiatrist must learn from the teacher, as the teacher must learn from the psychiatrist, but both of them should learn from the children with whom they are working.

Dr. Robert A. Matthews: Would Dr. O'Brien say a word here about the problems he meets in the teacher group, rather than among the pupils?

Dr. Milton K. Meyers: I wonder whether this public psychiatry has infringed in any way on private practice. The school system provides for public care; this might interfere with the child guidance departments of the university and with private psychiatric practice.

DR. FRANCIS O'BRIEN, New York: In answer to Dr. Meyers' question about the possible infringement of our services on the private practice of other psychiatrists, I may say that my colleagues and I have had no complaints from either psychiatrists or the psychiatric departments of hospitals. The most important reason is that about 99.9 per cent of the children with whom we deal have a hard time to get enough to eat, let alone pay private psychiatrists. Although there are eight units of the Bureau of Child Guidance in New York city involved in this work, we have scarcely scratched the surface. The problem is huge.

In reply to Dr. Bond's question about the definition for education, which I used, I may say that sociologic terms may seem too broad. However, the definition itself is of a kind that may well be accepted in a democratic society.

Why people go into educational work is an interesting question. It is somewhat like the situation in psychiatry, in which many people believe that psychiatrists must be a little queer themselves to choose mental illness as a specialty. No definite types of persons go into educational work, as the factors leading to the choice of education as a profession are many and varied. It is true that education offers a relatively unique situation in that a person acquires a position of authority without actually earning it, as compared with other professions, in which one attains a position of authority only after one has earned it. The fact that the teacher spends a good deal of her time in a superior position, dealing with immature human beings, must have some effect on her. It is difficult to know in what proportion these multiple factors enter into the problem. I believe, however, that the profession itself has a strong influence on the teacher's personality once she has entered it.

In educational circles there is too much of the giving and the carrying out of orders. There should be a great deal less of this, because teachers are apt to become too dependent on regulations and do too little thinking for themselves.

There have been some problems of adjustment, of course, between the various professions involved in the psychiatric care of children. Perfect cooperation between the social workers, the school teachers and the psychiatrists is difficult to obtain in the beginning. School people have a tendency to use the clinic as a channel of getting rid of difficult children. Consequently, when they are provided with an interpretation of the child's behavior and a practical program in which they are to participate, they frequently dislike the psychiatrist, as well as the child they referred.

In regard to Dr. Matthews' question about the personality of teachers in general, I think it is only fair to say that they have not been studied, as far as I know, but that on the whole they are not much different from 30,000 persons in any other profession. Of course, one finds some problems that seem to be unique. I know of no other group that carries so many home responsibilities. Many teachers find themselves in the position of caring for aging parents and other relatives because their brothers and sisters have married. Carrying too many financial and family responsibilities, putting nieces and nephews through college, thus keeping the nose to the grindstone, and always associating with younger minds, is bound to do something to them. Furthermore, dealing with children all day long under a rigid supervision, with little or no attention to creative social life afterward, has its effect on a great number of teachers. Possibly a greater number of teachers than members of any other profession lead unhealthy lives in that respect. A teacher who is dealing with thirty or forty children all day long, in a metropolitan school, where social, economic, racial and intellectual achievement levels are varied, should plan to do something that is personally satisfying and recreational when she gets out of her schoolroom. There is a great deal to be done in attacking these problems, which are really occupational hazards.

What is meant by a good teacher? There is much more to be said about teaching than competence in instruction, the marks children receive, discipline, grades, curriculum and courses. The teacher should be selected carefully as to her

personality. Sometime ago I was asked to outline what I considered essential to a good teacher. I described six or seven types and indicated how a step below or a step above might make an undesirable teacher. The problem of determining personality fitness is a difficult one and offers a real challenge to psychiatry and psychology.

As psychiatrists we must prepare ourselves if we are to contribute to education. Above all, we must approach the new opportunities that education offers with the conviction that we have as much to learn from educators as we have to contribute. In this spirit of cooperation, psychiatry and education will afford greater opportunities for each child to attain the highest possible level of physical, mental, moral and social health.

NEW YORK NEUROLOGICAL SOCIETY AND THE PHILADELPHIA NEUROLOGICAL SOCIETY

ABRAHAM A. BRILL, M.D., *President, New York Neurological Society, in the Chair*

Joint Meeting, April 7, 1942

Laurence-Moon-Biedl Syndrome. DR. S. PHILIP GOODHART, New York.

Within the past few years literature on this syndrome has been enriched. The complete syndrome—retinitis pigmentosa, polydactylism and syndactylism, dystrophia adiposogenitalis, oligophrenia and hereditary implications—is of rare occurrence. Up to 1928 there had been reported some 20 cases in which the six cardinal symptoms were represented. Originally described in 1866 by two English ophthalmologists, Laurence and Moon, the significance and implications of the syndrome were not recognized until over fifty years later. The problems of greatest interest and implication relate to the pathogenesis and heredity. Reports suggest that the syndrome, whether complete or fragmentary, is not due to a fortuitous or random combination of defects of genetic origin.

In the case presented here, a man aged 22, of Polish Jewish extraction, has been under observation at Montefiore Hospital for about eight years, having been admitted in 1934. The hospital records show no other case of the complete syndrome ever observed there. The patient presented all the classic features of the syndrome. The parents were first cousins; the family history, in the immediate antecedents, showed a pronounced hereditary taint. The mother passed through a psychotic episode of five months' duration after the birth of the patient; 2 paternal uncles and 1 aunt had pulmonary tuberculosis; a maternal uncle was institutionalized with schizophrenia. The only sibling of the patient, though of low average intellect, was not abnormal. Nothing is known of the possible occurrence of fragments of the syndrome in the forebears. The patient was born by breech delivery without untoward incident; he weighed 6 pounds (2,721 Gm.) at birth and up to his second year showed no mental abnormality. It was then observed that difficulty in his seeing objects and groping movements indicated defective vision. The poor vision was doubtless due to retinal changes. Recovery was complete from attacks of pertussis, chickenpox and measles in early life. Mental retardation was noted on his admission to school, and the patient was placed in an ungraded class. At the age of 9 years a temporary period of polyuria and polydipsia occurred, with rapid increase in deposits of fat on the breasts, abdomen and hips. Of interest is the contrast in the clinical picture at the time of admission to Montefiore Hospital, at the age of 14, and that at present, at the age of 22 years. At the age of 14 the patient was 4 feet 10 inches (147 cm.) in height and weighed 144 pounds (65.3 Kg.); he was rather short of stature and

obese, of the Fröhlich type. The skull was brachycephalic, measuring 21 inches (53 cm.) in circumference, at the fronto-occipital plane. The hair was of fine texture and abundant on the head and was entirely absent over the pubis and in the axillas; the palate was high arched and the teeth slanted inward; the gonads were far below normal size; the right testicle was undescended and the left small and soft; the penis was small. The fingers were short and tapering; the right hand showed polydactylism and syndactylism; the second and third toes of both feet showed syndactylism. The results of neurologic examination were essentially negative. The blood pressure was 110 systolic and 80 diastolic. The ophthalmologic changes were characteristic of the condition: marked reduction in vision, nyctalopia, divergent strabismus and a constant coarse nystagmus, but no muscular palsies. The pupils were eccentric and reacted normally. The disks were pale and vertically oval, and the retinal arteries were extremely thin. Around the periphery of each fundus were scattered deposits of superficial pigment; there was atrophy with disorganization of pigment in both maculas. The visual fields could not be studied accurately, but central vision and color distribution seemed to be absent in both eyes.

Roentgenographic examination of the skull, including the sella turcica, showed no gross pathologic changes. The right hand showed polydactylism, with six fingers, the extra digit being in the region of the fourth finger and consisting of a rudimentary metacarpal bone and three well formed phalanges, which articulated. Syndactylism between the toes was present, and the phalanges were narrower than normal. Roentgenographic examinations in 1932, 1936 and 1942 revealed the same condition.

Laboratory examinations at various intervals during the eight years of hospitalization showed that the chemical constituents of the blood and urine were normal. The basal metabolic rate varied between —17 and —31 per cent.

Mental examination showed definite retardation, with notable improvement during the eight years in the hospital.

A remarkable feature of the clinical picture was the decided change in gonadal development and the growth of hair of masculine type on the pubis, abdomen and legs. There is only 1 other case in the literature in which this degree of improvement in genital development appeared. This change did not seem to bear a direct relation to the administration of various endocrine preparations.

Lantern slides demonstrated the physical features, and the patient was presented.

A brief review of the genetic influence and the hereditary characters concluded the presentation.

DISCUSSION

Dr. A. M. Ornsteen, Philadelphia: Obesity of the Fröhlich type, with genital deficiency, is not uncommon, but when it is associated with mental defect and pigmentary degeneration of the retina the attention of the clinician is attracted.

In my study of the symptom complex my prime interest was to determine, if possible, even though on hypothetic grounds, the cause of the striking association of Fröhlich's dystrophy, pigmentary degeneration of the retina and mental deficiency. Polydactylism and other skeletal defects have been observed in about 60 per cent of cases—certainly less consistently than the other components of the symptom complex. In families with the Laurence-Moon-Biedl syndrome isolated defects or fragments of the complex, such as polydactylism, obesity, mental deficiency and retinitis pigmentosa, may be identified as genotypic characters in nonaffected members of the family.

My concern, then, was to explain why retinal changes, obesity and hypogenitalism and mental deficiency are so uniformly combined in this symptom complex, while in only about one-half the cases skeletal defects occur. I think the combination may be looked on as an inherited, genotypic unit character defect. In looking for an embryologic explanation, I was impressed with the close association of the hypothalamus, the forebrain and the peripheral visual system in the ectopic

zone of the prosencephalon, and I suggesed that a unit character defect arising from a single defective gene might explain the constancy of the clinical symptom complex so far as mentality, vision and the hypothalamic defects are concerned. Polydactylism, syndactylism and occasional impairment of hearing and other anomalies, such as atresia ani, might be explained, I postulated, on an accidental coupling of somatic genotypic defect characters with the cerebral unit character aforementioned.

This view was objected to by subsequent investigators, who offered the explanation of translocation or dislocation of a second defective gene in the same chromosome. However that may be, the practical aspect of this question is the identification of Fröhlich's dystrophia adiposogenitalis, without ocular or mental changes, as an inherited genotypic unit character defect, as differentiated from primary endocrinologic changes, which are common in children.

A slide shows 3 siblings with the cerebral unit character defect, namely, obesity of the Fröhlich type, mental deficiency and pigmentary degeneration of the retina; none of them shows skeletal defects. The boy of 12 presents the classic Fröhlich dystrophy, but if it were not for the history of hemeralopia one's attention would not be drawn to the Laurence-Moon-Biedl symptom complex. This child has genu valgum and pes planus, similar to the condition Dr. Goodhart reported in his case. This bone defect is not interpreted as inherited because such orthopedic features are prominent in both forms of Fröhlich's dystrophy. All 3 children show nystagmoid rolling of the eyes, which could be caused by the visual defect rather than by involvement of the cerebellovestibular pathway. The roentgenogram of the sella turcica is without important changes and presents evidence in keeping with the consensus that the earlier hypothesis of a high, massive dorsum sellae pressing on the infundibular stalk is not tenable.

The next picture shows the fundic changes in this disease—annular arrangement of pigment, optic nerve atrophy and small vessels. In the ascendants of this family obesity was a prominent feature of the history, but no one had hemeralopia or polydactylism.

The picture of the next patient, a child, shows only Fröhlich's dystrophy, without the other indications of the Laurence-Moon-Biedl syndrome. The next case is that of a very young girl who has prematurely enlarged breasts but who otherwise presents the hypopituitary picture of the Fröhlich type. She has a marked mental defect but is without retinal changes or skeletal anomalies. In the first case the clinical condition is probably the ordinary Fröhlich dystrophy, while the girl, in all likelihood, has the cerebral unit character defect of hypothalamic deficiency with mental arrest. Yet her condition is not to be looked on as a form of the Laurence-Moon-Biedl complex, since there is nothing in the siblings or in the ascendants to indicate familial implication either with this syndrome or with a concomitant unit character defect.

Intermittent Attacks of Fever Occurring for Thirteen Years in a Patient with Migraine. Dr. Stewart Wolf Jr. (by invitation) and Dr. Harold G. Wolff, New York.

A case is presented in which the patient suffered for many years with periodic sick headache and for thirteen years with frequently recurring bouts of fever, with a temperature up to 41 C. (105.8 F.). At intervals during this time he was hospitalized and was carefully studied at three large institutions. An infectious, neoplastic or metabolic cause for his fever was never demonstrated; indeed, he showed no loss in weight, debility or other evidence between attacks of being physically ill. Numerous therapeutic measures were ineffective in halting the attacks. A personality study revealed that he was suffering from an obsessive-compulsive neurosis, characterized by marked anxiety in a setting of insecurity and conflict following important defeats which he was unable to accept. He was given an opportunity to ventilate his conflicts and some aid in resolving them.

During this regimen his recurrent attacks of fever stopped, and he had neither fever nor headache for nearly a year. Finally, while living in another part of the country, where it was no longer possible to follow him closely, the patient suffered a brief recurrence of his intermittent fever. This occurred in a setting of unusual tension and anxiety. The bouts of fever are believed to be due to temporary derangement of the thermoregulatory centers of the brain, possibly of a vascular nature, arising in a setting of anxiety and insecurity in a rigid, compulsive person who has had migraine.

DISCUSSION

DR. HAROLD D. PALMER, Philadelphia: I have gone over some of the data on migraine which my associates and I have accumulated to see whether the records contain any information on severe disturbances of temperature regulation. In about 270 cases there were many in which answers to our questionnaire indicated that the patients had subjective feelings of heat and thought they had some fever, but in only 2 cases was there any significant rise of temperature, that is, up to or slightly above 100 F. In neither of these cases was the slight rise of temperature dissociated from the attack of migraine, and so it was not a migraine equivalent. Some rise of oral temperature may be expected in the presence of severe vasodilatation. In about 60 per cent of cases during the prodromal stage there were, among other symptoms, feelings of chilliness, coldness of the extremities, pallor of the skin and the appearance of goose flesh. We are, of course, familiar with Dr. Wolff's excellent work on the vasomotor dynamics of migraine; I do not know whether Dr. Wolff and his associates have studied the peripheral vasomotor changes of the skin during this prodromal phase, but with such symptoms of cold there must be considerable constriction of the superficial vessels of the skin. Since the sympathetic centers in the hypothalamus are believed to regulate the caliber of cutaneous blood vessels, I should like to ask Dr. Wolff whether he feels that the extreme vasomotor changes in migraine, or in certain equivalent phenomena, might be due to the action on the hypothalamus of a toxic substance in the blood stream. The theory expressed by Dr. Wolff of probable constriction of the vessels to and about the hypothalamus which sets off the peripheral vasomotor reaction, resulting in the rise of temperature and the various vasomotor changes, may be entirely adequate; yet toxic processes are known to affect the hypothalamic centers. Certainly, many of the other migraine equivalents, such as loss of vision, hemiparesis, aphasia, hemianopia and hemianesthesia, must be the results of transient vascular changes in the brain itself. Vasoconstriction would reduce the blood supply to the areas of the brain specifically related to the symptoms. In our experience in the treatment of migraine, many patients who are relieved of the severe headache phenomena have during the course of their improvement a wide variety of migraine equivalent states. There have been curious psychic equivalents marked by episodes of unreality and strangeness, pseudoangina, hemianopia, fortification spectrums and scotomas—all unassociated with headache. These, and other manifestations, must have their basis in some localized vasomotor change. The effect of psychotherapy seems to have been remarkable, but I should like to ask what other methods were used. Was dilantin given before, during or after the psychotherapy? Was ergotamine tartrate tried and, if so, when and with what results? One is struck by the resemblance between the periodic fevers in the case reported and some of the severe allergic manifestations. The allergic theory would not seem to apply in this case, however, because of the pronounced leukocytosis and the absence of eosinophilia. Dr. Wolff must believe that the hypothalamus is the chief mediating factor in the fevers, but I should like to hear him discuss further the possible causative factors other than the psychologic. There can be no doubt that in certain psychosomatic states the somatic changes secondary to psychogenic causes have to be brought about through the hypothalamus.

A number of cases have been reported in which the roentgenograms of the skull showed hyperostosis frontalis interna and in which the clinical syndrome was marked by sleep disturbances, excessive thirst and migraine headache. The headache was said to be relieved by ergotamine tartrate. It was thought that in these cases the osteophytes acted as a focal irritant in the hypothalamic region. Did Dr. Wolff's patient show any such hyperostosis? In the case presented there was obviously an extremely rich psychopathology.

Operative Treatment of Torticollis, Athetosis and Paralysis Agitans.
DR. TRACY J. PUTNAM, New York.

While the surgical treatment of the dyskinesias is still in a stage of rapid change, certain procedures have become reasonably well standardized.

The form of dystonia most surely susceptible to surgical treatment is spasmodic torticollis. In most instances operation is to be considered only when the pattern of movement is typical, when the disturbance of movement has been severe over many months, when the patient is largely incapacitated, when the Rorschach test fails to show evidence of hysteria and when psychotherapy has failed. These criteria are fulfilled sooner or later in the majority of cases.

The operation recommended is a modification of that first proposed by Foerster in 1918, with variations introduced by Dandy, Dowman and others. It consists in intradural destruction of the first three anterior cervical roots and the spinal accessory nerves on both sides. The first slip of the dentate nucleus has to be severed in order to get at the first root. A tiny cautery, heated to 80 C., is a useful instrument for destroying roots, with minimum danger of bleeding. If relief is incomplete, section of both accessory nerves in the neck or of the fourth cervical root on one side is performed in addition.

Operation for relief of athetosis is much less satisfactory. Cortical excision gives variable results, but usually increases the incapacity. Cauterization of the anterior column seldom results in any increase of disability, and the proportion of favorable results is about the same as with the cortical operation. The danger to life is somewhat greater, but not strikingly so.

Alternating tremor may be relieved, or greatly reduced, by operation on the pyramidal tract, apparently at any level. The easiest and safest procedure is to cut the lateral pyramidal tract at the second cervical level. This operation can be carried out only on one side. Only a minority of cases are suitable for operation. They are those in which a unilateral tremor is the most incapacitating feature of the disease and bulbar symptoms are minimal. Sometimes rigidity is strikingly benefited; more often it is not. The disability is surprisingly small in most instances.

DISCUSSION

DR. TEMPLE FAY, Philadelphia: Dr. Putnam has done things the rest have not; I can only add certain impressions from what I have seen and heard—certain convictions of my own chiefs and, in a few instances, observations from my own experience.

I have been privileged to hear Dr. W. W. Keen, at his own table, discuss his original operation designed to relieve torticollis and some of the dystonic types, and I recall the views expressed by Mills, Spiller, Dercum and Lloyd. Many here heard the brilliant debate between Ramsey Hunt and Mills on posture and tone in the early days of the Association for Research in Nervous and Mental Disease. I have seen the influence of Hunter and Royal come and go. Tayor, in 1915, first suggested a modification of the Keen operation, advocating the intraspinal approach to the upper cervical nerves, as well as to the spinal accessory nerve. In 1918 Foerster offered further modification of this operation, and then Sherrington suggested the possible influence of the posterior roots on spasticity and tone. In 1921 Finney advised section of the posterior branches of the motor roots, and

sometimes obtained good results in cases of spasmodic torticollis when the first, second and third cervical branches were divided. It will be recalled that Spiller urged destruction of the posterior roots in the upper cervical region, and in 1924 McKenzie suggested a combination of anterior and posterior root section. Frazier, in analyzing the problem in 1930, pointed out that although the location of the lesion was probably in the neostriatum, bilateral destruction of anterior and posterior roots, along with the spinal accessory nerve, was required to control this symptom complex. Frazier avoided the fourth cervical motor root because of its influence on respiration through the phrenic nerve. Dandy's paper appeared almost simultaneously with Frazier's; he also advocated section of the anterior and poserior roots in the upper third or fourth cervical segments, along with the spinal portion of the spinal accessory nerve. Dandy later modified his operation to include peripheral attacks on the problem as well.

In spite of reports that many of these surgical attacks greatly improved the condition, new procedures have constantly been sought because the end results have not been entirely satisfactory.

I am impressed with Dr. Putnam's simplification of the procedure by anterior chordotomy, but I do not feel that this or any of the preceding operative procedures are entirely rational.

I noted a great change in the movements of the patients as they were presented, especially the Negro, from those shown in the moving picture, taken earlier. In the case of the Negro, I am not convinced that the movements were those of true dystonia; their onset was so sudden and the posture so dramatic. The result, therefore, might be classed as psychotherapeutic if this patient's condition was originally functional.

Encephalomyelitis Optica: Report of a Case. DR. FOSTER KENNEDY, New York.

At the end of October 1931, a woman aged 34 experienced malaise and acute frontal headache, followed in three days by blurred vision in the right eye. Three days later vision in the left eye became reduced, and within a week she was blind on the right side and vision was greatly impaired on the left. Ten days after the onset of this illness light perception was absent in the left eye.

On November 18 shooting pains appeared in the lower extremities, together with numbness, tingling and hyperesthesia, and she experienced terrific pain in the bladder. There was a sense of loss of power creeping up the legs. By November 28 there were total flaccid paralysis of both legs, overflow retention of urine, paralysis of the rectal sphincter and loss of pain and temperature sensation up to the nipple line; position, vibration and deep perceptions were retained. Within a few days sensory loss ascended to the clavicles and both arms became flaccid.

On December 2 conjugate movements of the eyes were limited; within a week they vanished. The neck was stiff. The spinal fluid contained 63 lymphocytes per cubic millimeter and 84 mg. of protein and 40 mg. of sugar per hundred cubic centimeters. The diaphragm was paralyzed for two days.

On December 8 complete deafness was noted in the right ear, and two days later, in the left. At this time there was a return of temperature sensation over the trunk and the Babinski response was observed bilaterally. All reflexes had previously been abolished.

On December 13 pallor of both nerve heads was noted, and ocular movements returned to 75 per cent of normal function. The sensory level was at the mid-dorsal region. On December 16 the patient became lethargic and aphonic, but within three days she was able to talk, heard well on the right side, moved both legs and the right arm and perceived light with the right eye. Within a week she could move both legs, sensation returned to the lower extremities and she could hear with both ears.

Three weeks later slurred speech was again noted, and within six hours speech became unintelligible. Two days later she was mentally confused. By January 20 speech was clearer. When she raised her head from the pillow she involuntarily jerked it backward and slowly rotated it to the left. This disturbance disappeared after several days. Motor power in both arms had improved steadily.

On January 22 there appeared weakness of the right side of the face of peripheral type, and two days later she became comatose and both sides of the face were paralyzed. She was again unable to move any of the extremities. Tube feeding was required. On February 3 it was clear that spastic cerebral paralysis of the right arm and leg had been imposed on the recovering spinal paralysis. On February 7 the optic disks were paper white, and involuntary laughing and crying occurred. One week later she could move the right arm and could speak a few words clearly, but pseudobulbar laughing continued. Conjugate movements of the eyes returned, but weakness of the right sixth nerve appeared. On February 20 she complained that her left hand had been getting increasingly numb for a week and that the left side of the face was numb. Five days later left cerebral hemiplegia was noted, but on March 1 she could move the left leg slightly; little by little the hemiplegia improved, as did her general condition, including bladder control. However, on April 2 there was sudden loss of strength in the left arm and leg, which lasted a few days. On April 16 it was certain that vision was definitely improving, although the optic nerve heads remained white. On April 18 she had improved to the extent of being able to sit on the side of the bed, and one month later she could walk a few steps unsupported. Bladder control was greatly improved; speech was clear; behavior was somewhat hypomanic; at times even color appraisal was acute.

Over a period of four months she gradually improved in every respect, so that today the reflexes are normal and she can swim, walk, ride and dance. She is also able to read large type.

DISCUSSION

DR. SAMUEL B. HADDEN, Philadelphia: Dr. Kennedy has clearly presented a case of encephalomyelitis optica—a condition which many believe to be a clinical entity, that is, an acute infectious disease of the nervous system characterized by involvement of the optic nerve and the upper part of the spinal cord, probably due to a virus infection. I do not believe that this picture can be regarded at all times as a clinical entity, with a single etiologic agent—a virus. Other factors may produce the syndrome. I shall report the case of a patient in my service at the Philadelphia General Hospital, who was admitted on Feb. 4, 1941. Almost the only history of importance was that approximately a year earlier the patient had had a laparotomy because of intense abdominal pain, believed to be due to a gallbladder crisis. Operation revealed a comparatively normal gallbladder, without stones. The wound healed with great difficulty. In the light of later events I believe this is significant. Four days before his last admission to the hospital he began to experience difficulty with vision. Two days later his vision was so severely impaired that it was necessary for him to discontinue his work as a grinder in a saw factory. The same day he had paresthesias in both upper and lower extremities, and before long he had increasing difficulty in walking and increasing dimness of vision. On the fourth day he was totally blind and was paralyzed in both lower extremities. On admission to the hospital the diagnosis of encephalomyelitis optica was considered, but it was felt advisable, because of his occupation, to make examination for poisoning with heavy metals. Examination of specimens of the blood and urine revealed no lead but a high cadmium content. Subsequent studies confirmed the unquestionable evidence of intense cadmium poisoning. Investigation revealed that the patient came in contact with cadmium, magnesium and other metals in the processing of the saws with which he worked. Magnesium and similar metals may have caused the slow healing of his laparotomy

wound. This man did not have the stamina of Dr. Kennedy's patient and died on the fourteenth day after admission.

Autopsy revealed nothing of importance in the visceral systems but showed definite evidence of optic nerve atrophy and a pronounced degree of involvement of the spinal cord, with demyelination of practically all pathways. In effect, he had complete transverse myelitis at the level of the fourth dorsal segment. The demyelination was characterized by astrocytic gliosis. In my opinion, this patient, who clinically had encephalomyelitis optica, was suffering from acute cadmium poisoning. Examination of his spinal fluid revealed mild pleocytosis, and nothing else of particular importance. I believe one should not regard this condition at all times as an etiologic entity. It is my feeling that cadmium and other forms of metals, and possibly other conditions, may produce a similar clinical picture.

ILLINOIS PSYCHIATRIC SOCIETY

WALTER H. BAER, M.D., *President, in the Chair*

Regular Meeting, Dec. 4, 1941

Use of Preliminary Curarization with Electric Shock Therapy. DR. PAUL T. CASH, Omaha, DR. C. S. HOEKSTRA, Philadelphia.

The introduction of convulsive shock treatment by Meduna, in 1935, has provided an important new therapy in psychiatry, particularly effective with the depressions. The best technic to be used in the clinical application of the treatment is still in the stage of development. It seems certain that the beneficial factors are contained within the grand mal seizure but that the accompanying muscular violence plays no beneficial role. It is important, therefore, to suppress as far as possible the physical convulsion.

The first direct successful attempt to eliminate the physical convulsion was made by Bennett in 1939, when he introduced the use of curare with metrazol. Curare was found to be a safe, nontoxic, effective drug with a specific action at the myoneural junction, blocking motor impulses. It eliminated the traumatic hazards of the metrazol convulsion but did not detract from the effectiveness of the treatment. Several other drugs, such as quinine methochloride, beta erythroidine hydrochloride and magnesium sulfate have been used, but all have definite disadvantages.

The development of the electric shock method was the next important modification of convulsive therapy. The advantages are less post-treatment nausea and vomiting and reduction of excitement states to a minimum. Post-treatment confusion is not so profound. The aura associated with metrazol has been eliminated, and the fear of treatment, although still present in modified form, has been abolished to an extent which alone makes this method preferable to metrazol therapy.

The claim that fractures and dislocations do not occur with the electric shock method is erroneous, as shown by the accumulating reports of serious skeletal accidents. It is also important to note that trauma in the form of damage to the soft tissues has received little attention. The severe physical convulsion is still an undesirable and dangerous feature of the treatment. For this reason we have continued to use curare with the electric shock method. The result is that in the 139 cases in which the combined method was used there were no fractures or dislocations, and complaints of muscle soreness and backaches were eliminated. Results in this series compare favorably with those obtained with curare and metrazol and with metrazol alone. The treatment is most effective with the

depressions, for which it acts as a near-specific therapy. The percentage of complete recoveries is greater in the older age groups.

It is emphasized that convulsive therapy in itself does not constitute a treatment but that strict psychiatric management and intensive psychotherapy are essential if the best possible results are to be obtained. The ambulatory method of treatment is to be condemned.

DISCUSSION

DR. LLOYD H. ZIEGLER, Wauwatosa, Wis.: It may be well to compare in general the experiences of Dr. Cash with those my associates and I have had at the Milwaukee Sanitarium. Since Sept. 26, 1940 we have treated 167 patients with electric shock. They have received a total of 1,485 shocks, or an average of 8.9 treatments per patient. (We do not like to give more than 12 electric shocks to one patient until we know more about the method.) Eleven of these patients were given 86 treatments combined with curare. This constitutes 5+ per cent of the treatments, or 6 + per cent of the patients. During the same time 4 patients were given 35 metrazol shocks—with 10 of which curare was combined.

Earlier in our experience with metrazol shock a few of our patients experienced fractures and dislocations, but it was soon learned that these complications could be prevented, except in the rare case, by controlling the patient's posture during a seizure. As can be seen, we have largely abandoned the use of metrazol, chiefly because electric shock seems to have all the therapeutic advantages of the metrazol method, is more easily administered and is not remembered so unpleasantly by the patient. Whether its use carries with it hazards not to be found after metrazol therapy has not been conclusively proved. It is known that metrazol shocks, among other things, induce gliosis of the brain when given too frequently. Reports of pathologists and experimenters indicate that lesions may appear in the brain after a moderate number of electric shocks. It is well known that epileptic persons at times suffer intracranial vascular lesions, and there is much presumption that injuries to the blood vessels result from the violent convulsive movements. Such vascular lesions may be responsible for the proliferation of glia to be found subsequent to a long series of metrazol or electric shocks or epileptic convulsions.

The reason that we have not used curare routinely in our shock treatment is twofold. Early in our experience we could not get all of the curare we needed. Then it developed that by controlling posture the drug did not seem to be necessary. We reserve its use for some persons over 60, especially those who are undernourished, whose bones are much decalcified, and for those of any age who have had well defined osteoarthritis. We use it also with persons who have, or have had, fairly severe hypertension or whose blood vessels are known to have been damaged. We gave it to a young man whose shoulder joint was deformed and was dislocated easily.

Fracture-dislocation complications have not been encountered in the last 1,000 electric shock treatments we have given. We are not so concerned about protecting the bones, joints and intervertebral disks as we are about conserving the vascular tree, from the capillaries to the heart itself. We have seen an old, unrecognized endocarditis flare up after shock. Quiescent tuberculosis has been known to be activated. We have not had such a complication. An old glaucoma became active in 1 of our patients after 5 or 6 shocks. Two patients had the second, and even the third, convulsion within two hours after a metrazol seizure. This has not occurred after electric shock. Memory and orientation are regularly disordered after metrazol or electric shock, the disturbance being more severe in some patients than in others. Without more than our own clinical observations to bear on this, we agree with Dr. Cash and Dr. Hoekstra that electric shock affects these functions more than metrazol and that it persists longer. We have thus far seen no patients in whom this memory defect has not largely cleared up in two months. This is one of the sequelae that bears watching. We have had 2 deaths that could be attributed to shock therapy.

As for results, we feel that those the authors have obtained with schizophrenia are better than our own. There are many factors that might conspire to make it so. Our results with the depressions are much like theirs. With manic states our results are distinctly better than theirs, and the reason for this may rest in the method we employ. We are encouraged by the results they have had with neurotic patients. While we feel that the treatment may be worth a trial with alcoholic addicts, we have not been encouraged by our results with such patients. We have not felt that patients with outspoken constitutional psychopathic states were rendered harmless by anything but chronic wise supervision.

The shock treatment methods have caused the psychiatrist more nearly to approach the surgeon in his point of view. The therapies are not cure-alls, but they serve to boost the patient's energies to the point where psychotherapy can be carried on. Every patient must learn sooner or later to live within his resources, and with wisely cultivated outlets, if therapy is to succeed. I agree that shock treatment of outpatients is to be condemned.

To know their intrinsic worth, these so-called drastic therapies must be evaluated after five to ten years or more. At present they offer the most hopeful immediate relief from functional psychoses. While we at the Milwaukee Sanitarium do not see fit to use curare routinely, we recognize it as a most valuable protective agent to be used with selected patients. While we have not used any of the many other protective agents now available, from what we have seen in other clinics and have read, taking into account the lethal range and the ease of administration, we believe that curare is one of the best, if not the best.

Dr. Victor Gonda, Chicago: It is regrettable that in such a fine statistical study as that presented here an important point has been missed, namely, the duration of illness of the schizophrenic patients receiving electric shock treatment. It is by now an established fact that the results are far better when the treatment is started soon after the mental symptoms appear.

It is my impression that in many cases the electric shock treatment was prematurely terminated. More worth while results could be obtained with a larger number of shocks, especially if followed by adequate psychotherapy.

May I ask Dr. Cash whether he used the fairly safe quinine preparation instead of curare, and, if he did, what were his experiences with it?

Finally, did he use the shock treatment for alcohol addicts as a means of helping them to stop drinking or only when there were signs of alcoholic psychosis, as an aid in ameliorating these complications?

Dr. Paul T. Cash, Omaha: Of the other drugs used to modify the convulsive seizure, at least three should be mentioned. First, Dr. Gonda referred to quinine methochloride. This makes a satisfactory substitute, except for two factors. First, the quantity of the drug used is large, 25 to 35 cc., and this makes an awkward procedure. Second, there is a rather constant drop in blood pressure, which is best to avoid if possible. Although a good "curare effect" is obtained, the margin of safety is not as great as with curare. Another drug is beta erythroidine hydrochloride. Unpleasant side effects, such as the early appearance of "head symptoms" and dysarthria, accompany the use of this drug. Depression of respiration is apparent before the injection is completed. A longer period of post-treatment confusion and at times severe respiratory depression occur. The use of magnesium chloride has recently beeen reported. Here, again, are certain disadvantages. The quantity of the drug required is between 25 and 35 cc., and the administration is accompanied by a peculiar sensation in the throat, flushing of the face and profuse diaphoresis. The "curare effect" obtained is less than that with curare, and less adequate protection is afforded.

Dr. Gonda has mentioned the advisability of a greater number of treatments, particularly with the more resistant depressions and with schizophrenia. We have never employed the treatment to the extent that he speaks of. Possibly a larger

number of treatments is indicated in certain cases. With regard to patients with chronic alcoholism, I wish to emphasize that they were treated because of prominent anxiety or depressive features.

We believe that it is necessary to obtain a certain amount of confusion in order to gain the desired therapeutic result. Some patients, after 6 to 7 treatments and a rest period, show little confusion and may have a partial relapse. A few more treatments produce definite confusion and a satisfactory recovery. It is apparent that a certain amount of confusion is desirable and in some way is related to the improvement effected by the treatment.

WALTER H. BAER, M.D., *President, in the Chair*

Regular Meeting, Feb. 5, 1942

Effect of Benzedrine Sulfate on Migraine: A Preliminary Report. DR. JACQUES S. GOTTLIEB, Iowa City.

The purpose of this report is to describe the effectiveness of benzedrine sulfate in the treatment of attacks of migraine. The justification for the use of this drug depends on the studies of Wolff and his associates. They have shown that dilatation and distention of cranial arteries, irrespective of how produced, form the basis for the headaches. According to their experiences, both benzedrine sulfate and ergotamine tartrate reduced the amplitude of pulsations of the cranial arteries. Since benzedrine sulfate has fewer toxic manifestations than ergotamine tartrate, it was decided to test this drug in adequate amounts to learn whether it was effective in aborting, reducing or terminating attacks of migraine headache.

Twenty-five patients suffering from typical migraine, but free from other discernible disease, formed the basis of this report. Of these, 18 received the drug intravenously in doses of 3 to 20 mg. The drug was injected cautiously at the rate of 1 mg. per minute in the first injection. Subsequently, if no untoward symptoms developed, the speed of injection was increased to the point of causing a rise in blood pressure of from 20 to 40 mm. of mercury, since this seemed necessary for the drug to be effective. These 18 patients were treated for 51 paroxysms. Twelve, or 66 per cent, consistently obtained complete relief from their attacks in seven to forty-five minutes. The concomitant pharmacologic effect of the drug, besides causing a rise in both the systolic and the diastolic blood pressure, was a variable increase or decrease in the pulse rate, usually the latter, dilatation of the pupils and pallor of the skin. In 1 patient cardiac irregularity characterized by extrasystoles occurred.

Twenty-two patients were instructed to take from 10 to 40 mg. orally at the first sign of the onset of the paroxysm. Of these, only 8, or 36 per cent, received relief consistently. They suffered from typical but infrequent and mild attacks.

In contrast, 3 patients having severe and frequent attacks responded well to benzedrine sulfate when it was given intravenously. The frequency of their paroxysms, however, was such a serious problem that it was decided to try oral administration of the drug as a prophylactic measure. Small oral doses were given during the day and night, and a maintenance dose was determined for each patient which relieved the symptoms, yet was not sufficient to cause any toxic manifestations. An illustrative case history is presented.

DISCUSSION

DR. DONALD MORRISON, Oconomowoc, Wis.: Graham and Wolff have shown that constriction of the temporal and middle meningeal vessels produces relief from the pain of migraine; I wonder whether Dr. Gottlieb has assumed that it is by such constriction that benzedrine sulfate relieved the attacks in his patients. It would be unfortunate if, because benzedrine sulfate proves to be effective, as Dr. Gottlieb has pointed out, the theory of the vascular causation of migraine should be reenforced, for, despite the great emphasis that has been put on changes in the blood vessels as the cause of migraine, it is questionable whether one can really explain the seizures on this basis. The vascular theory is one of the most popular today; yet it leaves many facts unexplained. It does not account for the symptoms due to disturbances of the cranial nerves. It does not explain emotional reactions in attacks of migraine, and it does not state how an emotional discharge, such as sudden rage, can abruptly terminate a migraine seizure.

One is in a better position to speak of the psychologic factors in migraine than to discuss the organic changes which are responsible for them. A good deal is known about personality and something about the precipitating factors, but very little is known about the organic side of the attacks. There has been some discussion as to whether changes in the nerve cells are not primarily responsible for the attacks and whether vascular changes are merely secondary effects. As is known, benzedrine sulfate is useful in other disorders. It is effective in the treatment of narcolepsy, and there is some evidence that it may be useful in depressive states. I wonder whether the fact that it has these different effects does not open up the possibility of finding out something more about the central causes of migraine. Does Dr. Gottlieb think that other effects than the possible vascular changes produced by the benzedrine sulfate may explain the relief of the migraine—that there is some central action which may be responsible for the help obtained in his cases?

Dr. Gottlieb did not say anything about the personality of the patients. It was not particularly relevant to his paper. I wonder, however, if it did resemble the type that is generally described. In regard to the patient who had migraine since the age of 3 years and then was completely freed of the attacks, I should like to know whether she had definite changes in her personality at the time she experienced relief—whether, for example, there was a change from a depressive trend to a euphoric state.

DR. PERCIVAL BAILEY, Chicago: If Dr. Gottlieb believes that the relief from migraine is caused by constriction of the temporal and meningeal arteries, how does he explain that ligating these arteries does not stop the pain?

DR. JACQUES S. GOTTLIEB, Iowa City: I hesitate to discuss the first problem Dr. Morrison raised, that concerning the pathogenesis of migraine. Certainly, irrespective of the primary cause of the attack, there are vascular changes of angiospasm or dilatation. Whether the pathogenesis is vascular or whether these changes are only physiologic concomitants I cannot say. The vascular theory, which has had its adherents for many years, finds considerable support in the careful experimental results of Wolff and his associates. It has always seemed that the primary arguments in favor of the central theory of the causation of migraine rest on the unanswered question of how it is possible for many of the unusual symptoms and migraine equivalents to be produced by vascular changes. In line with this is Dr. Bailey's question. I do not know why ligating the vessels supposedly involved does not relieve the attack. Dr. Bailey's experience is much greater than mine in this regard, and I accept his observations as fact. I had, however, been under the impression that ligation of the involved vessels relieved the attacks of pain in that area, but that subsequent attacks continued to occur in some other location.

In answer to Dr. Morrison's second question, it seems fairly certain that benzedrine sulfate has a central action as a stimulant. It can be used effectively

to terminate narcosis and to produce a delay in the desire for normal sleep. It frequently produces improvement in mood, which includes feelings of augmented energy, relief of fatigue, increased confidence, general expansiveness and even euphoria. There is possibly a slight quickening of mental processes, more evident subjectively than objectively, which probably is a reflection of the change in mood rather than any real augmentation of innate intelligence. Just how the benzedrine sulfate acts is not known. Two theories have been advanced, namely, (1) that it stimulates the cortex directly and (2) that its action is distributed over the entire symphathetic nervous system.

In regard to the personality of patients suffering from migraine, I can only reiterate what has been stated many times before. Their personalities seem to conform to a general type. Usually they are serious, conscientious, worrisome, tense and with their goal pointed toward perfection. In the case of the patient who received benzedrine sulfate by mouth, no change was noted between her behavior prior to the development of her severe symptoms and her behavior after she had become symptom free with medication.

News and Notes

SOUTHERN PSYCHIATRIC ASSOCIATION

The annual meeting of the Southern Psychiatric Association will be postponed for the duration of the national emergency because of the request for restricted travel by governmental agencies, because of the large number of members who are now serving in the armed forces and because of the greatly reduced personnel in the institutions served by the older members of the association. The roster of officers and members will be frozen, and all dues will be suspended until the emergency has passed. In the meantime the secretary of the association requests that he be kept informed of any change in address of members and that he be advised of all matters pertaining to the welfare of the association.

Book Reviews

Goals and Desires of Man. By Paul Schilder. Price $4.00. Pp. 305 + XII, with index. Columbia University Press, New York, 1942.

Volumes still flow from the pen of this neuropsychiatric encyclopedist, thanks to the thoughtful remembrance and enthusiasm of his friends, organized as The Paul Schilder Memorial Fund Committee. There will be much interest in "a psychological survey of life" by one who led so busy and productive a career in eager pursuit of new insights into human nature.

The author pays great respect to Sigmund Freud, not only in direct statements but also indirectly through formulating his own final opinions about the goals and desires of man in the form of comments and criticisms about psychoanalytic concepts. A consideration of aggressive and destructive impulses leads to the denial of a death instinct, and an affirmation of the primacy of constructive impulses, to which the destructive are considered secondary and contributory. He discusses incidentally the constructive elaboration of the body image, putting much emphasis here upon protrusions and openings, acknowledging the importance of sexual symbolization but asserting the importance also of nonsexual meanings, such as nutrition. Four chapters are devoted to the discussion of attitudes toward death—rather eerie reading in a posthumous publication.

After death come nine chapters on sex—a curious temporal inversion which serves to emphasize the highly abstract manner in which the author deals with "the problem of biography," which was set as the central theme of the book. "Sex seen from the point of view of biology represents incompleteness with the urge to become complete again," page 117. "Most of the characteristics generally considered feminine and masculine have nothing at all to do with the actual difference between the sexes," page 212. More particularly he denies that activity and passivity are characteristically masculine or feminine.

In a chapter on Morals, emphasis is again placed on the principle of the integrity of other persons. "We want the same full relations to the world in others as in ourselves." Advice to a patient is requoted as the conclusion to this chapter: "The indefiniteness and complexity of moral laws make a variety of preliminary solutions possible."

There are also chapters on Tools and Economics, Property, Danger Situations, Work, Ideologies and Conclusions. The 32 conclusions are, in part, the orderly outcome of the data and discussion but in larger part represent an attempt to compress into aphorisms principles not systematically considered in the body of the book. The aphoristic style, which pervades the book, is unfortunately not always very logical, even when expressing sound principles, e. g., page 280, "Experience is social in every form; this is proved by the fact that perception is inseparably connected with action."

The chapter on Ideologies represents, in the reviewer's opinion, Schilder's most characteristic and effective thinking about human life. In it occurs this paragraph, page 234: "Human life circles around a limited number of basic problems, which must be mastered not only from the point of view of emotion but also from the point of view of intellectual insight. The problems that must be liberated from merely verbal involvement to completeness are: Body and beauty; health, strength, efficiency, superiority and inferiority in a physical sense; aggressiveness and submission, masculinity and femininity; the relation of sex and love; the expectation for the future; the meaning of death."

Essentially, we have in this book a series of footnotes to Freud, by an intelligently industrious critic.

The Creative Unconscious; Studies in the Psychoanalysis of Art. By Hanns Sachs. Price, $2.75. Pp. 240. Cambridge, Mass.: Sci-Art Publishers, 1942.

For many years Dr. Sachs has been interested in the exploration of the problems of esthetics. To this end he has employed the methods and theory of psychoanalysis. The result is this book of essays on problems related to origin of the artistic, creative urges. The first two chapters treat of the creative act, starting from daydreams as the most common form of fantasy. The next three chapters illustrate, respectively, how genius picks up a time-worn piece of material and transforms it into a masterpiece, the effect of inhibition on civilization and the influence of infantile fantasy life. The fifth chapter discusses the development of Freud's scientific mind in the light of his life experiences, especially as revealed in his book "The Man Moses."

Chapters VI to IX are concerned with the central problem of esthetics, discussing what beauty is from several standpoints: poetry, painting and music. The mental mechanism that produces artistic satisfaction may be schematically described as follows: The author gives to his repressed wishes the form of fantasies which appeal to the unconscious of his audience; their own repressed wishes are the same as his; he is brought out of his isolation, and his guilt feeling no longer makes him feel like an outcast; it becomes a bond between him and his audience. The element of beauty comes in because the author of a work of art feels isolated during his period of inhibition and therefore gives to his production, where it is set free, all the narcissistic compensation for his self elimination. Play is also an important element; it gets rid of the censorship of the superego by letting the author feel that he is safe as long as he is "only playing make-believe."

Such psychologic explanations of beauty and art are rightly considered by the author as conjectures at the present time, but they give to students of esthetics a new, and no doubt an important, angle from which to approach their subject. For the psychiatrist, the book is of interest because it brings out the interesting examples of fantasy among artists and geniuses that so closely resemble neurotic and schizophrenic reactions.

A Bibliography of Aviation Medicine. By E. C. Hoff and J. F. Fulton. Price, $4. Pp. 237; no illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

This is a timely and scholarly contribution, containing references to almost 6,000 articles, which cover every aspect of aviation medicine. The articles are grouped in a logical manner according to main headings and subheadings. The volume is beautifully printed and bound.

Of particular interest to the readers of this journal are the sections on neuropathology, neurology and psychiatry. The references to work in the field of neuropathology are rather scanty, and a number of important articles are omitted, such as those dealing with the effects of hanging and the more important papers on carbon monoxide poisoning.

To judge from the contributions to neurology and psychiatry, which are few, a great opportunity is open for further advances. The application of modern technics of electrophysiology and psychometrics to the problems of aviation on a large scale has apparently been neglected. In the present emergency, no time should be lost in making use of them.